Clinical Research Publications on Fetal Alcohol Spectrum Disorders 1985-2025

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The Brain in the Fetal Alcohol Syndrome

Observations in Human and Nonhuman Primates

Sterling K. Clarren, M.D.
Douglas M. Bowden, M.D.
Susan Astley, B.A.

It has been difficult to try to establish a dose-response curve for fetal alcohol syndrome (FAS); but it is likely that, generally, FAS occurs in the offspring of women who are chronic alcoholics. Still, fetal alcohol effects may occur in babies born to women who binge drink or who consume more modest amounts of alcohol. In fact, human and nonhuman primate studies on brain structure and function now strongly suggest that gestational alcohol consumption can effect fetal brain structure and function even in the absence of any external morphologic change such as facial abnormalities or disruption in growth (characteristic of full-blown fetal alcohol syndrome).

A project now under way in our laboratories should help to strengthen the clinical impression that fetal alcohol effects occur in the absence of fully developed fetal alcohol syndrome and to clarify the dose-response curve to some extent. The study will also offer behavioral, neuropathologic, and neurochemical correlations that should provide new knowledge of brain function and may even suggest some more appropriate behavioral therapy or drug intervention for children whose behavior is affected by gestational alcohol exposure.

Characteristics of FAS in Humans and Primates

Youngsters with FAS are microcephalic at birth, (Microcephaly is a condition chracterized by abnormal smallness of the head, usually associated with mental retardation.) Newborns with FAS are usually irritable and tremulous. They often suck poorly and frequently show discomfort with sensory stimulation of any kind. Infants who are intoxicated at birth (due to maternal alcohol consumption prior to delivery) will metabolize ethanol extremely slowly because they are deficient in hepatic ethanol dehydrogenase (the principal enzyme for metabolism of ethanol).

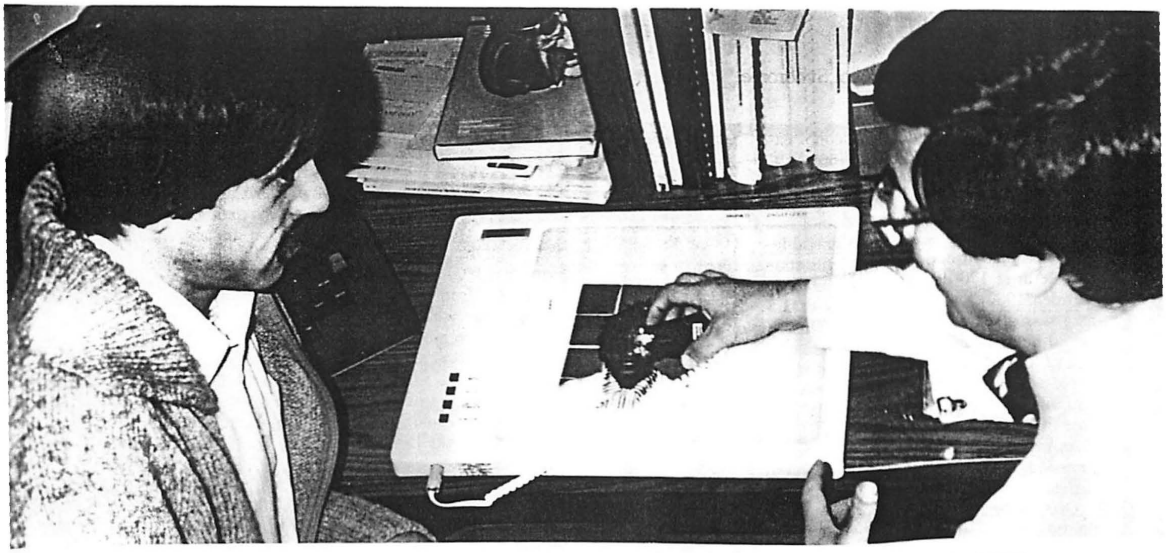
Older children are generally hypotonic (have diminished tone of the skeletal muscles) and are poorly coordinated in motor control. Hypertonicity (a condition in which skeletal muscles exhibit abnormally high resistance to passive stretching) is occasionally noted and may lead to a diagnosis of cerebral palsy, a persisting motor disorder caused by nonprogressive brain damage. Seizures have been rare, although neurological abnormalities may be noted through brain wave recordings using electroencephalography. Increased minor motor movements are nearly always found. These movements seem most typical of FAS children and interfere with their ability to concentrate on any specific learning task. Behavioral therapy and drugs like methylphenidate (a central nervous system stimulant often used in the treatment of hyperkinetic children) have not been successful in controlling this form of hyperactivity.

Only 16 brains of children known to have been exposed to high gestational volumes of ethanol have been reported in the medical literature. The first autopsied study was included in the initial work on FAS by Jones and Smith (1973, 1975). The brain was then included with three others studied by Clarren and colleagues (1978). Clarren found that all four brains displayed similar malformations stemming from errors in migration of brain cells, both neural and nonneural. Hydrocephalus (a condition characterized by an abnormal increase in the amount of fluid in the cranium, causing enlargement of the head and destruction of the nerve cells in the brain) was one consequence of the malformations in two of the infants.

Clarren (1981) later published an additional case. This brain was small in size and was marked by reduction in cerebral white matter (composed of nerve cell fibers), and disorganized migration of nerve cell bodies along the surface of the lateral ventricles (the fluid-filled cavities in each cerebral hemisphere of the brain).

While Majewski and colleagues (1978) reported a normal autopsy in a stillborn exposed to alcohol, Peiffer and colleagues (1979) reported six autopsied cases of FAS with neuropathologic findings. Finally Wisniewski and colleagues (1985) reported five neuropathologic assessments in patients exposed to gestational alcohol. Their examination of the five FAS infants revealed microencephalic brains in all cases, without structural evidence of delay in the brain's maturation. One of the examined brains showed agenesis (absence) of the corpus callosum (the bridge of nerve fibers that facilitates communication between the left and right cerebral hemispheres) and hypoplasia (underdevelopment) of the cerebellar vermis (the middle portion of the twin-lobed cerebellum). Five of the brains studied had only small dysgenetic (defective developmental) changes.

The brains examined in these studies, then, showed similar patterns of brain deformities and lesions. Early errors in migration of embryonic brain cells to their proper positions led to diffuse patterns of malformation in all cases. Later



Drs. Sterling Clarren (right) and Paul Sampson analyze facial features of children known to have been exposed to alcohol during gestation (See sidebar on next page).

gestational exposure presumably produced destructive lesions of the cerebral white matter in a third of the patients (see Table 1). These findings are extensively discussed elsewhere (Clarren and Bowden 1982).

What is of interest to this discussion is the relationship of those brain malformations to the patients' overall appearance. Table 2 shows the clinical features of FAS and neurologic abnormalities. Of the 16 children, 7 would have received the FAS label because they exhibited growth deficiency, the "FAS face," associated malformations, and brain dysfunction. Two of these children had extreme patterns of brain disruption, while five had more mild structural neuropathologic problems. The other nine children would have been labeled clinically as possibly or probably afflicted by fetal alcohol effects because none had a clearly alcohol-related appearance. Indeed, one child was apparently normal. In spite of this, three of these nine children had a severe form of brain disruption. Clearly, then, it is not clinically possible to declare a child free of alcohol-related problems just because growth or appearance is normal.

Attempts to Measure Fetal Risks

Several problems have made it difficult to establish risks to teratogenesis (the production of physical defects in offspring prior to birth) from maternal ethanol consumption. Usually, alcohol consumption has been measured through self-reporting, which is always of uncertain validity. In addition, patterns of drinking vary daily in most people; and it is unlikely that any two human fetuses have ever been subjected to exactly the same exposure pattern. Besides, alcohol absorption and metabolism vary considerably in adults, so fetuses may be exposed to differing conditions despite similar maternal consumption. Finally, accurate assessment of alcohol teratogenesis from study of the individual's appearance (assessing genetic *and* environmental factors) is clearly inadequate.

In order to assess more fully the relationship of altered body structure to brain

Table 1. Neuropathologic Change in 16 Patients with Fetal Alcohol Effects

	Severe	Mild
Cerebral Malformation 14/16		
Neuroglial heterotopias	2	10
Cortical dysgenesis	3	7
Nuclear dysgenesis	3	2
Agenesis of corpus callosum	3	1
Agenesis of anterior commissure	1	1
Cerebral White Destruction 5/16		
Hydrocephalus ex vacuo		6
Periventricular leukomalacia		1
Cysts		1
Cerebellar dysgenesis 10/16	4	6
Brainstem dysgenesis 4/16	3	1

Table 2. A Comparison of Clinical Features of Fetal Alcohol Syndrome to Neuropathologic Alterations in 16 Case Reports

Dysmorphic Pattern	Severe Brain Alteration	Mild Brain Alteration
Face/Growth/Malformations (FAS)	2	5
Face/Growth	2	1
Face/Malformations	—	2
Face	1	1
Growth		1
None		1

structure, brain function, and alcohol exposure, we developed a model for investigating alcohol-related birth defects in the pigtail macaque *(Macaca nemestrina)*. In a pilot study, ethanol was given just once per week to four gravid female macaques from 40 days of gestation until term at 170 days (Clarren and Bowden 1982). A dose of ethanol of 2.5 g/kg was given to three animals. This would be equivalent to human consumption of about 6 drinks at a time and yielding a peak serum ethanol level of about 250 mg/dl. Another animal received a dose of 4.1 mg/kg, which would be equivalent in humans to about 10 drinks at a time with a peak serum level of about 350 mg/dl.

One moderate-dose animal miscarried; the others all carried to term. The high-dose infant macaque was found to be dysmorphic (suffered congenital malformation) and mentally retarded. The brain in this infant at 6 months of age was extremely malformed in many ways similar to those seen in humans afflicted with FAS. The moderate-dose animals appeared to be normal, although one was mildly retarded and the other had borderline normal intelligence on standardized measures of primate performance. At autopsy, however, small neuronal heterotopias (displaced or misplaced tissue) were found in the brain of the mildly retarded animal. In moderately exposed and control animals, the caudate and the putamen (two regions involved in control of body movements) were studied. Dopamine, the principal neurotransmitter in these regions was found to be abnormally active in both of the experimental animals.

The FAS Face

There is no question that the facial characteristics indicative of fetal alchol syndrome change over time from infancy to adolescence and into adulthood. Therefore, if health care professionals are to make the diagnosis of FAS in children at different ages, they need to know what the face looks like at various stages in a child's development, says Sterling K. Clarren, M.D., of the University of Washington School of Medicine.

To help identify precisely what facial features indicate a diagnosis of FAS past infancy, Dr. Clarren and his colleagues have collected photographs of 42 7-year-olds known to have been exposed to alcohol during gestation and are now analyzing their facial similarities with a computer-aided technique called digitization.

Digitization is a process that analyzes geometrical relationships among specific facial features. Specifically, Dr. Clarren and colleagues are studying triangular relationships among the inner and outer angles of the eyelid, the eyebrow, the outer points of the nose and the lips, and a series of points along the lateral aspect and center of the face.

Preliminary results suggest a new description of the "FAS face."

"Prior descriptions of facial characteristics of FAS based on clinical examination have always indicated that the midface of FAS children was the right size, but that their nose was short," Dr. Clarren says. "That's probably wrong. Our studies now indicate that the nose of such a child is probably the right length but that the midface is long. We now have evidence that the chin appears to recede in these children as well."

Clearly a long midface and a short chin are two important features which could be helpful in diagnosing the syndrome, Dr. Clarren says.

—Doug M. Podolsky

The Current Investigation

We have now undertaken a study involving 36 gravid pigtail macaques exposed to a wider range of alcohol dosage. This study will not be completed until 1986 and only one-half of the animals have been fully assessed to date. Still, some trends in the results can be disclosed at this time.

In the current project, the weekly oral exposure to alcohol begins in the week following timed mating—a month before pregnancy is confirmed. In general, it is estimated by the University of Washington Primate Center that 50 percent of females are confirmed pregnant after timed breeding when there is no human interference. The rates of implantation of the fertilized egg in the uterus was found in Table 3. Statistical assessment will not be

Table 3. Implantations in Primate FAS Project After Weekly Alcohol Exposure from Week #1 As of April, 1985

Peak Maternal Serum Ethanol Level mg/dl	Cohabitations	Confirmed Pregnancies	%
0	12	6	50
20–30	23	7	30
40–60	15	6	40
100–120	15	6	40
150–200	12	5	41
250–290	7	4	57
350–700	17	5	29

Table 4. Pregnancy Outcome in Primate FAS Project After Weekly Alcohol Exposure from Week #1 As of April, 1985

Peak Maternal Serum Ethanol Level mg/dl	Pregnant/ Delivered	Abortion	Liveborn	%
0	6/6	1	5	83
20–30	7/5		5	100
40–60	6/5		5	100
100–120	6/5		5	100
150–200	5/1	1		0
250–290	4/4	3	1	25
350–700	5/5	4	1	20

Table 5. Subjects in Primate FAS Project After Weekly Alcohol Exposure As of April, 1985

Peak Maternal Serum Ethanol Level mg/dl	Liveborn	Live Fetus	Total
0	5	0	5
20–30	5	1	6
40–60	5	1	6
100–120	4	1	5
150–200	0	4	4
250–290*	3	2	5

**Weekly alcohol exposure after gestational week #4.*

Table 6. Neuroscience Investigation in Primate FAS Project

Standardized macroscopic & light microscopic eval.	
R cerebral hemisphere	S.K. Clarren, M.D.
R cerebellum	Univ. of Washington
Dopamine activity measured by spiroperidol binding	
L striatum	H. Lai, Ph.D.
	Univ. of Washington
Electron microscopic eval.	
L gyrus rectus	K. Rudeen, Ph.D.
L preoptic region	Univ. of Missouri
L calcarine cortex	
L striatum	
Monaminergic neurotransmitters: Epinephrine, Norepinephrine, Dopamine, Seratonin	
L gyrus rectus	W. Shoemaker, Ph.D.
L anterior hippocampus	Univ. of Connecticut
L striatum	
L preoptic region	
L calcarine cortex	
Semi-quantitative histofluorescence	
hypothalmus	J. Sladek, Ph.D.
	Univ. of Rochester
Neuronal morphology & dendritic proliferation	
L hippocampus	J. West, Ph.D.
	University of Iowa

done until the study has been completed. Nevertheless, it appears that alcohol affects either conception or implantation at even the lowest levels of weekly exposure to ethanol. The confirmed pregnancy outcomes are shown in Table 4. In the control group and in the lower weekly-ethanol-exposed groups, the fetuses have nearly all been carried to term without difficulty. However, in the high-exposure groups, most of the fetuses have miscarried. In order to bring sufficient fetuses to term, we have adjusted the study as noted in Table 5.

Gravid macaques assigned to dosage groups achieving peak serum ethanol levels below 200 mg/dl receive their first dose with the first week of conception; animals who will achieve a peak serum ethanol level above 200 mg/dl do not receive their first dose until pregnancy is confirmed at 40 days' gestation. The study will be completed when six animals in each serum level category have been fully studied.

With the exception of the weekly dosing, the animals' pregnancies are normally maintained and the animals are observed for weight gain and health. Food intake is monitored daily and is withheld on the morning of dosage. The alcohol (20 percent solution in water) is delivered through a tube inserted through a nostril and extending to the stomach. The animals that serve as controls are given the same amount of sucrose solution that contains the same number of calories as the ethanol dose. The infants are delivered vaginally at term unless medical indications warrant ceasarian section.

After the birth of an infant macaque in the project, a standard set of measures are obtained. These include standard facial photographs, cephalometric radiographs (an x-ray image of the anatomic structures of the head), and such anthropometric measurements as size, weight, and proportion of the head; body size; and foot size. Sensory assessments include examination of the interior of the eye, tests for detailed vision, and studies of brain waves evoked by sensory stimulation. Over the first 6 months of life, the infant animals are tested on numerous standardized scales of primate intelligence and development, including neonatal reflex assessments, infant motor milestone scale, social milestone scale, object-permanence (cognitive) scale, and visual pattern recognition.

At the age of 6 months, various biochemical and neuroanatomical stuides are performed. The studies and the investigators involved in this part of the project are listed in Table 6.

Conclusion

It is as yet premature to make any firm statements about the results of the current investigation, although we do expect to find behavioral changes and pathological system changes at doses lower than those needed for observable body structure changes. We also anticipate finding biochemical changes in the brain that may be correlated with behavioral changes. □

Turn to page 73 for references.

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Pregnancy Outcomes After Weekly Oral Administration of Ethanol During Gestation in the Pig-Tailed Macaque (*Macaca nemestrina*)

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ABSTRACT Ethanol was orally administered once per week to gravid pig-tailed macaques (*Macaca nemestrina*) in doses of 0.3, 0.6, 1.2, 1.8, 2.5, 3.3, or 4.1 g/kg. A control group received a sucrose solution, isocaloric and isovolemic to the highest ethanol dose. Pregnancy was followed after 116 possible conceptions in 54 females. Peak plasma ethanol concentrations (PPECs) ranged from 24 ± 6 mg/dl at the 0.3 g/kg dose to 549 ± 71 mg/dl at the 4.1 g/kg dose. An increased rate of spontaneous abortion was related to ethanol exposure at and above 1.8 g/kg (mean PPEC = 205 mg/dl). Pregnancy failure in the first 30 days of gestation increased at doses above 2.5 g/kg. The effect on pregnancy outcome of weekly exposure to ethanol in this nonhuman primate is comparable to available data on humans. The methodology of this study represents an effective model for studying ethanol teratogenesis in a nonhuman primate.

The morphologic and behavioral teratogenicity of alcohol has been well documented in humans (Clarren and Smith, '78). Deficits associated with intrauterine ethanol exposure include diminished growth, increased rates of major anomalies, structural brain anomalies, developmental delay, and behavioral problems. The fetal alcohol syndrome (FAS) represents the full manifestation of intrauterine ethanol exposure. Partial FAS phenotypes and other patterns of dysmorphogenesis are not clinically diagnostic of alcohol teratogenesis but may in fact be causally related. These alternate patterns have been referred to as "possible fetal alcohol effects" or, more recently, "alcohol-related birth defects."

In spite of intensive review of human ethanol consumption during pregnancy, no dose-response curve for ethanol teratogenicity has been established. The reports of alcohol consumption from mothers of infants with FAS are not sufficiently accurate to determine the "dose." Individual variations in consumption patterns of ethanol as well as variations in individual metabolism—both of the mother and of the fetus—further complicate experimental design. It is probable that there is no *single* dose-response relationship for ethanol teratogenesis, but rather that each abnormal outcome in brain structure or function, morphology, and growth has its own dose-response and gestational timing parameters.

There are a number of reasons for studying alcohol teratogenesis in a nonhuman primate model. A generally recognized principle of toxicologic research in animals is that no one species can perfectly model the human situation (Abel, '80). Several rodent models for studying ethanol teratogens have been developed. These models are useful in identifying the range of teratogenic effects, in elucidating the basic biochemical effects of ethanol on mammalian tissue, and in identifying potentially critical periods during gestation when the mammalian fetus is most vulnerable to specific toxic effects of ethanol. Such models are less useful in elucidating dose-response aspects of human FAS. Further, much of the rapid phase of brain growth that occurs in late gestation in humans occurs postnatally in rodents, which renders the small animal model inadequate for deter-

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mining the relationship between ethanol exposure and phenotypic changes in brain structure and function.

We have previously reported data from a pilot project in which ethanol was orally administered to four pregnant pig-tailed macaques (*Macaca nemestrina*) (Bowden et al., '83, Clarren and Bowden, '82). The ethanol was given just once per week in order to mimic human binge drinking (intermittent consumption). One animal received a dose of 4.1 g of ethanol per kilogram body weight, while three others received a dose of 2.5 g of ethanol per kilogram of body weight. These doses produced average peak plasma ethanol concentrations (PPECs) of approximately 400 mg/dl in the higher-dose animal and 250 mg/dl in the lower-dose animals. The treatment was initiated in each animal after the confirmation of pregnancy at about 30 days' gestation, and dosing continued thereafter once per week until delivery at about 170 days' gestation.

One of the animals given the 2.5 g/kg dose aborted on the 77th day of gestation, whereas the other animals carried to term. The pregnancies were largely uncomplicated. The infants underwent a variety of psychometric and developmental tests and were assessed anthropometrically and dysmorphologically. At 6 months of age they were killed. Each animal had a complete autopsy with neuropathologic study and several special neurochemical assessments.

The animal exposed to 4.1 g/kg of ethanol was facially dysmorphic and had severe developmental delay. Its brain was dysplastic, with anomalies similar to those previously reported in humans (Clarren et al., '78). The animals exposed to 2.5 g/kg of ethanol appeared morphologically normal, but one had evidence of developmental delay and had more subtle neuropathological anomalies.

The pilot project was conducted with only a few animals and rather large exposure doses, and the animals were not exposed to ethanol in the first 4 weeks of gestation, a period of rapid organogenesis. Nevertheless, the results supported the concept that different alcohol-related teratogenic outcomes could occur at differing ethanol exposures, with behavioral teratogenesis occurring at lower exposures than structural teratogenesis.

The pilot data encouraged us to pursue a more thorough study, and this project was initiated in October 1982. The present study retained the once per week ethanol exposure format of the pilot project, but dosing took place within the first 10 days of conception so that more of the embryonic period was teratogenically vulnerable. In addition, the size of the experimental population was increased, allowing for a wider range of dosing cohorts.

Each infant was assessed in sequential evaluations for growth by using specific protocols for anthropometric measures. Dysmorphology examinations were conducted directly and through standardized radiographs and photographs. A battery of developmental and psychometric tests was completed. At 6 months of age each animal was examined by necropsy, at which time the brain was removed and subdivisions were distributed to scientists who studied specific regions for gross and microscopic anatomy at light and electron microscopic levels. Finally, neurochemical analyses were made of comparable brain regions. The active research phase of this project reached completion with the necropsy of the last macaque offspring in June 1986.

This paper outlines the experimental design, the methods of dosing and assessing the dams, as well as the results that relate ethanol dose levels to gestational outcome. The results in terms of infant development and postmortem findings are being analyzed and will be reported in forthcoming articles.

MATERIALS AND METHODS

Fifty-four adult female pig-tailed macaques (*Macaca nemestrina*) were selected for this project from the breeding colony of the Regional Primate Research Center at the University of Washington. The criteria for selection included good health (normal physical exam, stable weight, normal complete blood count, normal urinalysis, normal serum chemical screen), age between 5 and 15 years, a history of producing at least one viable infant in the previous 2 years, and no unusual history of negative pregnancy outcomes (spontaneous abortions, stillbirths, or early neonatal deaths). These females were classified as low-risk breeders within the colony. The sires came from a group of 26 equally healthy males whose weights were within 1 standard deviation of the mean weight for age of male pig-tailed macaques and who had no evidence of high-risk breeding histories.

Females were mated at the inception of detumescence of the vulvar tissues, the time in their menstrual cycle associated with peak fertility. A laparoscopy procedure was performed within 36 hours of breeding to observe a corpus luteum and confirm ovulation. The laparoscope was inserted through a small incision in the abdominal wall after the animal was anesthetized with intramuscular ketamine, 10 mg/kg. The procedure was generally accomplished in 10 to 20 minutes, and the animal was usually fully alert after 1 hour.

When ovulation was positive, a random assignment to an ethanol dose cohort was given, and the animal began its weekly receipt of ethanol or control solution. Dosing was performed on all animals on the same day of the week. Upon confirmation of ovulation, the pregnant animal was dosed on the next day of the week set aside for dosing. As a result, all animals received their first dose within the first 10 days of gestation.

In our colony, pregnancy is confirmed by uterine palpation at 30 days' gestation. If palpation for pregnancy was negative 30 days after possible conception the mating was declared a failure—the female had either not become pregnant or there had been a direct or indirect embryotoxic event. Animals that were pregnant by palpation at 30 days were maintained in their dose cohort until a birth or spontaneous abortion occurred. Whenever a female was rebred for the project she was randomly assigned to a different dosing cohort. Female animals were removed from the breeding pool after a maximum of four negative palpations at 30 days' presumed gestation or after two positive pregnancies.

The ethanol doses were selected to produce PPECs in a range equivalent to the human range of light social drinking (20–50 mg/dl ethanol) to very heavy binge consumption (up to 600 mg/dl ethanol). Doses included 0.0, 0.3, 0.6, 1.2, 1.8, 2.5, 3.3, and 4.1 g/kg ethanol. The alcohol was diluted by volume in four parts water. A sucrose solution which was isocaloric and isovolemic to the highest ethanol dosage was given to animals assigned to the 0.0 dose group.

The initial study design proposed that breeding, cohort assignment, and dosing would continue until at least seven confirmed pregnancies were followed in each cohort. It was apparent from the outset that ethanol exposure initiated within the 1st week of gestation might interfere with conception or implantation or might be so highly embryotoxic as to significantly decrease the number of confirmed pregnancies in a cohort. We were therefore prepared to shift the dosage schedule and initiate dosing *after* the confirmation of pregnancy at 30 days gestation in any cohort found to be depleted by the early dosing. This procedure was necessary at and above the 2.5 g/kg dose. Animals treated only after confirmation of pregnancy are referred to as "delayed-dose animals," and a "d" is placed after their doses in the text and tables.

The day before each dosing session the animals were weighed, and the volume of ethanol or sucrose solution was calculated. The animals were denied access to food after 5 p.m., and a 24-hour fast commenced in preparation for dosing the following morning. On the morning of the dosing day each animal was brought unsedated from its cage and examined. The resting pulse was recorded, and the uterine height was measured. The dose of ethanol or sucrose was then slowly and carefully delivered over a 5-minute period through a soft nasogastric catheter (size 8, French). After dosing, the animal was returned to its cage and observed periodically. Food was reintroduced at 5 p.m. on that day.

Once every 8 weeks the dosing procedure was followed by a series of blood samples drawn by femoral venipuncture to determine the course of change in ethanol concentration. This was done by recapturing the unsedated animal periodically over a period of time sufficient to allow detection of the ascending and initial descending phases of the ethanol disposition curve. In the animals given 0.3 or 0.6 g/kg of ethanol, blood samples were obtained at intervals of 2, 10, 30, 60, and 150 minutes after dosing. In the animals given 1.2, 1.8, or 2.5 g/kg of ethanol, the blood samples were obtained at intervals of 30, 90, 120, 150, and 210 minutes after dosing. In the animals receiving the 3.3 or 4.1 g/kg ethanol doses, the blood samples were obtained at intervals of 30, 90, 120, 150, and 300 minutes after dosing. The timing of the samples was calculated so that the PPEC could be reasonably well gauged without undue stress from handling the animals. Samples were obtained over sufficient time after the period of peak ethanol concentration such that the remainder of the curve could be simulated by the MKMODEL program (Holford, '81) on the Prophet computer system (Bio-

technology Resources Program, '82). The computer simulation generated plasma ethanol concentrations at 9-minute intervals by using the following Michaelis-Menten equation (Kalhorn et al. '86a):

$$dC/dt = C_0 - [(Vmax\ C)/(Km + C)]$$

where C is the ethanol concentration at time t, Vmax is the maximum velocity of elimination, and Km is the apparent in vivo Michaelis-Menten constant. C_0 is the concentration at time zero, which in our analysis was the last measured plasma ethanol concentration in the elimination phase of each trimester ethanol curve. It is from this point in time that the subsequent course of ethanol elimination was projected by the Michaelis-Menton model. Km and Vmax values were set at 6.5 mg% and 24.8 mg%/hr, respectively. These parameter values were obtained in a pharmacokinetic study of ethanol elimination after intravenous administration to 11 *Macaca nemestrina* (Kalhorn et al., '86a). It was additionally known that the ethanol disposition curve following administration of 0.6 g/kg ethanol in the oral/fasting condition was very similar to that following the same dose in the intravenous/fasting condition (Kalhorn et al., '86b).

The blood samples (1.0 ml) were mixed with ethylenediamine tetraacetic acid (EDTA) and chilled on ice. Within 1 hour, the plasma from each sample was transferred to a 0.5-ml microcentrifuge tube and stored at − 70°C. Ethanol levels were determined from those samples by gas chromatography (Kalhorn et al., '86a) within 6 weeks of acquisition.

The animals were housed in individual cages adjacent to compatible animals in rooms with a general low level of activity. These placements served to minimize stress. The animals were fed 40 biscuits of Purina Monkey Chow daily, supplemented occasionally with a wedge of apple. Leftover biscuits were counted each morning to monitor food intake. As noted above, the biscuits were removed from the animals' cages at 5 p.m. the day prior to dosing, and food was not reintroduced until 5 p.m. on the dosing day. Even minimal food consumption can greatly influence PPEC (Kalhorn et al., '86b), and our procedure permitted the alcohol to be fully absorbed on an empty stomach. Only two animals ever became finicky eaters and decreased their normal food intake significantly over a day or two which was unrelated to dosing and was not accompanied by other signs of illness. These animals' diets were supplemented with a high-calorie supplement (Nutri-cal, Evsco Pharmaceuticals) until usual intake was restored.

When the animals were within 15 days of their estimated date of delivery, they were transferred to a labor and delivery suite where they were monitored for signs of labor every 30 minutes around the clock by closed-circuit television. When signs of active labor were observed, a member of the delivery team was called to attend the birth.

In animals exposed to alcohol from the 1st week of gestation, a decision to perform a caesarian section was made if the fetus maintained a consistent breech position after 160 days' gestation or if the pregnancy went beyond 180 days' gestation without any signs of labor. Caesarian sections were performed on all animals exposed to the very high doses (3.3d or 4.1d g/kg) to minimize perinatal loss in this very high risk group.

Pregnancy outcomes were classified as follows:

1) *Thirty-day pregnancy failure.* A corpus luteum was seen by laparoscopy within 36 hours of mating, but a negative palpation was recorded at 30 days' gestation. This could represent a failure in conception, an early embryotoxic event, or an implantation failure.

2) *Spontaneous abortion.* Any spontaneous termination of pregnancy from 30 days' confirmed gestation to 160 days' gestation.

3) *Stillbirth.* Delivery of a nonviable fetus after 160 days' gestation (In this study stillbirth was always associated with breech position).

4) *Viable infant.* Delivery of an infant with sustained cardiorespiratory function.

RESULTS

One hundred sixteen matings in 54 females were followed by a positive laparoscopy result. Thirty-day pregnancy failure did increase with increasing alcohol dose (Table 1). These rates for pregnancy failure in control and delayed-dose animals 30 days after possible conception are comparable to overall colony figures for pregnancy failure (50%) based on more than 1,000 timed matings. The pregnancy failure rates among animals

TABLE 1. Pregnancy failure at 30 days' gestation in pig-tailed macaques after weekly exposure to ethanol

Dose assignment (g/kg ethanol)	Dams bred	Thirty-day pregnancy failures	
		n	percent
Delayed dose[1]	23	12	52
Sucrose treated	14	7	50
0.3	21	14	67
0.6	16	9	56
1.2	15	9	60
1.8	14	5	36
2.5	6	5	83
4.1	7	7*	100

[1]No exposure to alcohol or sucrose within the first 30 days of gestation.
*P = .008 (binomial test).

TABLE 2. Pregnancy outcome after confirmation of pregnancy in pig-tailed macaques undergoing weekly exposure to ethanol

Dose cohorts (g/kg ethanol)	Confirmed pregnancies	Spontaneous abortions	Breech stillbirths	Viable infants
Sucrose control	7	1	1	5
0.3	7	—	—	7
0.6	7	1	—	6
1.2	6	—	1	5
1.8	9	3	2	4
2.5	1	1	—	—
2.5d[1]	3	1	—	2
3.3d[1]	3	—	—	3
4.1d[1]	5	4*	—	1
Totals	48	11	4	33

[1]Delayed dose, i.e., no exposure to alcohol in the first 30 days of gestation.
*P = .002 (binomial test).

receiving between 0.3 g/kg of alcohol and 1.8 g/kg of alcohol varied from 36% to 67%. These rates were not statistically different from the study control cases by binomial analysis. At the 2.5 g/kg dose, however, five of six animals (83%) had pregnancy failure. Although this rate was not statistically significant, it was higher than the rate at any lower dose and may be clinically relevant. At the 4.1 g/kg dose, 100% of the pregnancies failed, and this was significantly different from the study control group rate (P = .008, binomial test).

The abortion rate among low-risk, breeding, colony-born, single-caged *M. nemestrina* in the colony as a whole is 12–13% (Sackett, '86). The rate of spontaneous abortion increased to 33% at the 1.8 g/kg dose (Table 2). The only animal to become pregnant at the 2.5 g/kg dose also aborted. Among the animals in which ethanol exposure was initiated after 30 days' gestation, a significant increase in miscarriage rate to 43% occurred at the 4.1 d g/kg dose compared to controls, notwithstanding the small sample size (P = .002, binomial test).

Thirty-six animals carried infants to term: 25 delivered vaginally and 11 delivered by caesarian section. Three vaginal deliveries were complicated by unexpected breech positioning and stillbirth. One infant in breech position died in spite of an attempt to salvage it by caesarian section. One of the stillborns had been exposed to the control solution, while another was exposed to the 1.2 g/kg dosage, and two were exposed to the 1.8 g/kg dosage (Table 2). This rate of fetal loss from breech positioning (4/46 = 9%) is comparable to the overall colony rate of 6% in low-risk macaques (Goodlin and Sackett, '83). Thus, there was no evidence that the alcohol exposure changed the rate of breech positioning or stillbirth owing to breech positioning. Indications for caesarian section were randomly distributed as one or two pregnancies in all cohorts except the 0.6 g/kg and 1.8 g/

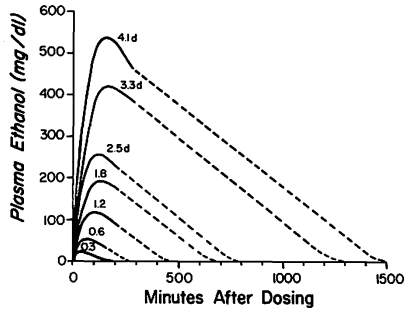

Fig. 1. An ethanol metabolism curve is displayed for each cohort. The numbers next to each curve signify the oral dose in g/kg. The solid portion of each curve represents the fit of observed plasma ethanol concentration within each cohort to the following exponential equation: $f(t) = A(e^{-tT_1} - e^{-tT_2})$, where A = plasma ethanol constant, T_1 = time constant −0.0083, and T_2 = time constant −0.02 (U.S. DHHS, '80). The dotted continuation of each curve is the computer-stimulated elimination phase based on the Michaelis-Menten equation: $dC/dt = C_0 - [(Vmax\ C)/(Km + C)]$.

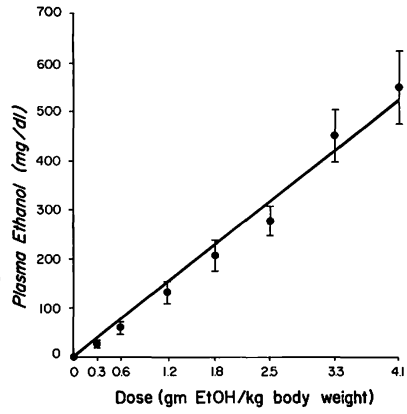

Fig. 2. The mean peak plasma ethanol concentrations with ± 1 standard deivation relate linearly to the ethanol doses. The number of animals studied in each cohort ranged from 4 to 8 with 6 to 16 individual ethanol curves used to calculate each mean and standard deviation.

kg cohorts, in which all births were vaginal, and the 3.3d g/kg and 4.1d g/kg cohorts, in which all four animals were purposefully delivered by section.

The average gestational length was 174 ± 9.3 days in controls and 172 ± 6.8 days in the experimentals pregnancies. The lack of significant differences at any dose (the norm for the colony as a whole was 171 ± 12 days) (Sackett et al., '75) indicated that ethanol exposure had no adverse impact on gestational duration. Neither did alcohol affect the usual nocturnal timing of labor.

The genetic background and physical condition of the animals did not appear to affect the distribution of pregnancy failures or abortions when examined independently of ethanol exposure. Twenty-three animals were bred once, 12 animals were bred twice, 13 were bred three times, and six were bred four times. Each multiply-bred animal was randomly assigned to a different dose cohort with each pregnancy. The distribution of possible pregnancy outcomes among animals with like-study parity was within an anticipated random distribution.

There were no consistent variations in the ethanol disposition curves of animals across the three trimesters. Moderate fluctuations in PPEC occurred in both directions over time. Such fluctuations were expected (Kalhorn et al., '86b).

Because stress may lower PPEC (Kalhorn et al., '86b), it was thought possible that our animals' PPECs could have been decreased through the handling involved in drawing the blood samples. Kalhorn has reported that animals receiving 0.6 g/kg ethanol orally had PPECs of 63 ± 12 mg/dl when nonstressed and 45 ± 6 mg/dl when stressed. The PPECs in our 0.6 g/kg cohort were 59 ± 13 mg/dl—essentially the same as in Kalhorn's fasted nonstressed animals.

The plasma ethanol concentrations for all animals within each cohort were plotted to produce an ethanol disposition curve that represented each dose cohort (Fig. 1). The area under each curve represents the "relative exposure" to ethanol. The mean PPEC at each dose level is displayed in Figure 2. The mean PPEC increased linearly with dose; the range of PPECs of most adjacent cohorts overlapped at the extremes. Unlike PPEC, the "relative exposure" to ethanol increased exponentially with increasing dose (Fig. 3).

The variation of PPEC within each cohort was examined in order to determine if ani-

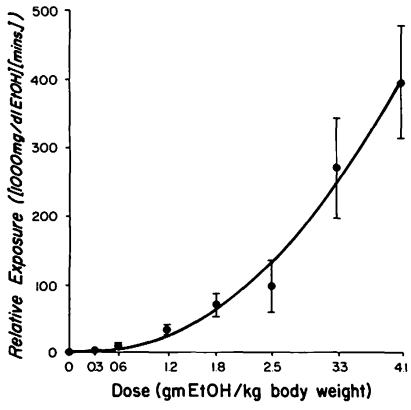

Fig. 3. The mean "relative exposure" to ethanol with ± 1 standard deviation relate exponentially to the ethanol doses.

mals that aborted had the highest PPECs within their dose-cohort. This analysis demonstrated that the abortions were randomly distributed within each group.

The medical records and feeding charts of the dams with pregnancy failures or abortions were examined for evidence of possible etiologic factors other than alcohol exposure. The general health of the dams was excellent, and illness was rare.

All of the animals that received the 4.1d g/kg dose markedly decreased their biscuit consumption on dosing days. Because of the caloric value of the ethanol, however, their overall caloric intake decreased by only 14% on those days, and the animals showed normal pregnancy weight gains.

It was not apparent that exposure to ethanol in any specific pattern of gestational days correlated with pregnancy failure. Animals dosed on gestational days 2, 9, 16, etc., 4, 11, 18, etc., or 7, 14, 21, etc., were all equally likely to have pregnancy failure or success.

The stress of the dosing procedure per se was examined by comparing the 30-day pregnancy-failure rate of the sucrose control animals with that of the delayed-dose animals who experienced no experimental handling until the confirmation of pregnancy. As reported above, pregnancy failures were the same in the two groups (50% vs. 52%), suggesting that the procedure did not induce conceptional difficulty.

At the lower doses of ethanol (0.3–1.2 g/kg), no behavioral change was apparent in the dams after administration. In the intermediate doses (1.8 and 2.5 g/kg), the animals became somewhat quieted, while the animals in the highest dose cohorts (3.3d and 4.1d g/kg) became ataxic, somnolent, and disoriented. One animal in the 3.3d g/kg cohort showed signs of nausea on one occasion. No animal ever became comatose.

DISCUSSION

Two groups of investigators have previously published reports of their efforts in developing primate models for studying ethanol teratogenicity. Altshuler and Shippenberg ('81) maintained constant (24 hour) plasma ethanol concentrations in pregnant rhesus monkeys (*Macaca mulatta*) by using permanent intragastric cannulae. They found that control animals and two animals with blood ethanol concentrations in the 75–100 mg/dl range carried fetuses to term, while two animals with blood ethanol concentrations in the 150 mg/dl range aborted. Jacobsen and coworkers ('80) used the long-tailed macaque (*Macaca fascicularis*) in a project designed to assess teratogenesis by maintaining constant blood ethanol levels with administration through permanent intravenous catheters. Unfortunately, high abortion rates and technical difficulties terminated the study. Jacobsen then trained 15 nonpregnant female animals to consume a diet including ethanol. Four of these females became pregnant and continued to drink. One of the fetuses aborted, one infant was growth retarded and possibly dysmorphic, and two infants were phenotypically normal. The blood ethanol levels were in the 20–50 mg/dl range when measured, but given the methodology, PPEC could not be reliabily or consistently obtained.

In our study we wished to use a dosing sequence that more closely modeled the typical human experience. Humans do not maintain constant plasma ethanol levels. Even the most chronic alcoholics drink intermittently within and across days. Thus we selected an oral rather than venous route of dose administration and a weekly exposure pattern similar to human "Saturday night

TABLE 3. Ethanol dose or alcohol beverage consumption[1]

PPEC	Oral dose ethanol (g/kg)		Equivalent liquor doses (fl oz) in 55-kg women		
(mg/dl)	Macaque	Human[2]	Whiskey[3]	Wine[4]	Beer[5]
24	0.3	0.2	1	3	8
59	0.6	0.4	2	6	16
130	1.2	1.0	5	15	39
205	1.8	1.5	7	23	59
277	2.5	2.1	10	32	83
431	3.3	3.2	15	49	126
549	4.1	4.1	19	63	161

[1]Required to attain peak plasma ethanol concentrations (PPECs) in human females equivalent to those obtained in pigtailed macaques.
[2]Calculated from formula: predicted PPEC(mg/dl) = 133.8 × Etoh dose (g/kg) (Dubowski, '76).
[3]Ethanol 50% by volume, 12 g/30 ml ethanol.
[4]Ethanol 15% by volume, 3.6 g/30 ml ethanol.
[5]Ethanol 6% by volume, 1.4 g/30 ml ethanol.

drinking." The dosing paradigm produced viable infants through the range of PPECs likely to be achieved in humans.

This report focuses on the study's experimental design, methodology of the prenatal phase, and the pregnancy outcomes. Ethanol was found to increase fetal loss independent of potentially confounding factors such as nutrition, stress, illness, or genetic background. When ethanol exposure began in the first 10 days of gestation there was an increased abortion rate at the 1.8 g/kg dose (PPEC = 205 mg/dl), and above the 1.8 g/kg dose, the pregnancy failure rate became nearly 100%. When ethanol exposure began in the 5th week of gestation there was a statistically significant abortifacient effect at 4.1 g/kg (PPEC = 550 mg/dl).

A follow-up study will be needed with larger animal numbers and more dose cohorts to fully establish if there is a threshold dose or a graded dose response for the fetotoxic effects of oral ethanol. Still, it is reasonable to assume that this effect from weekly alcohol exposure occurs only well above a PPEC of 100 mg/dl, the legal limit of intoxication in humans. In further relating these findings to women, several questions arise. Does the primate fetus experience the same ethanol exposure as its mother? Is macaque ethanol absorption and elimination comparable to human ethanol disposition? Is there evidence to corroborate that ethanol is fetotoxic in humans?

The maternal nonhuman primate PPEC has been found to be comparable to the fetal PPEC through gestation (Hill et al., 1983; Bowden, unpublished observations). Comparable ethanol levels are found in the mother and fetal units, although ethanol elimination is primarily done by the maternal liver.

Formulas have been developed that predict PPEC from the volume of ethanol ingested in humans. By using such a formula (Dubowski, '76), one can estimate the ethanol doses that a typical 55-kg woman would need to ingest to achieve PPECs comparable to those attained by the cohorts in this study (Table 3). The predicted dose estimates for human females are about one-third less than for macaque females at the lower PPEC levels and become equivalent with increasing PPEC. The calculated human doses of ethanol can be converted to fluid ounces of whiskey, wine, and beer (Table 3). Thus, to achieve a PPEC of 205 mg/dl, the PPEC level at which nonhuman primates in this study experienced an increased rate of spontaneous abortion, the average human female would need to consume seven standard drinks (7 fl oz hard liquor, 23 fl oz wine, or 69 fl oz beer) on a weekly basis. Such heavy intermittent alcohol consumption is not uncommon. A recent national survey measuring the drinking patterns of American women found that 2.7% of interviewees regularly drank six or more drinks once or twice per week (Wilsnack et al., '84).

Obviously, while the equivalences presented in Table 3 may be applicable to average macaque and human females, they cannot be applied directly to specific individuals. For example, the range of individual differences in the coefficient for estimating the dose required to produce a given PPEC in human females is more than ± 16% of the mean (Dubowski, '76). Thus, if an alcohol-tolerant human female achieves a PPEC of 205 mg/dl from 7 oz of whiskey, a few women may achieve that blood level at a dose of about 5 oz and a few may require 9 ounces. Other factors such as body weight, gastric contents, and stress, exert considerable influence on the PPEC achieved by a given oral dose (Kalhorn et al., '86b). Nevertheless, our data in nonhuman primates supports other data that suggest that women who drink to levels of marked intoxication on a weekly basis increase their risk of abortion.

The conversions presented in Table 3 can be quite useful in comparing findings from this animal model with the results of epidemiological studies that have aimed at determining levels of alcohol consumption that

may affect spontaneous abortion rates in the human. In a prospective study of 1,200 pregnancies, Sokol et al. ('86) reported an increase in abortions among "heavy drinking" women but did not clarify the specific consumption levels. Kline et al. ('80) reported a case-control study comparing the drinking histories of 616 women who aborted spontaneously with 632 women who carried their pregnancies to at least 28 weeks' gestation. The data suggested that a mean of two standard drinks twice weekly was the minimum threshold for producing an abortion. Harlap and Shiono ('80) prospectively assessed 32,000 pregnancies and reported a doubling of spontaneous abortions in the second trimester for women drinking one to two standard drinks per day on average.

In both of the latter quantitative studies, average alcohol scores were derived by estimating weekly consumption in terms of fluid ounces of absolute alcohol and then dividing by seven to obtain an average daily ethanol consumption in ounces/day (Jessor et al., '68).

The majority of macaques that aborted had mean PPECs above 200 mg/dl. An average human female would achieve a comparable PPEC by consuming five to nine standard drinks containing a total of 2.5 to 4.5 oz of absolute ethanol (Table 3). Such a weekly drinking pattern can be converted to an average alcohol score of 0.4 oz/day to 0.6 oz/day. This is similar to average alcohol scores that can be derived from Harlap and Shiono ('80) and from Kline et al. ('80), which placed the threshold for increased spontaneous abortions in humans at 0.5 oz/day and 0.3 oz/day, respectively.

The magnitude of fetal exposure to an environmental agent and the sequence or number of exposures are both potentially important factors in teratogenesis. The average alcohol score is one attempt at expressing the interaction of amplitude and frequency in ethanol exposure. While the conversion of a weekly consumption amount to an average daily consumption score produces reasonable agreement in the consumption threshold for spontaneous abortion and ethanol exposure between human and nonhuman primates, it raises a new question. Are all dosing patterns that produce an average daily exposure of the same magnitude equally abortifacient, or are some exposure patterns more likely fetotoxic than others?

One reason to suspect that a single large intermittent dose is more detrimental than the same dose distributed over time is seen in Figure 3, where relative exposure is observed to increase exponentially with dose. This reflects the fact that larger doses not only produce higher peak blood concentrations but require longer time periods to clear and thus extend the duration of exposure to ethanol following ingestion of a given amount. Although 1 oz of absolute alcohol consumed daily yields the same average alcohol score as 7 oz of absolute alcohol consumed once weekly, the relative exposure is considerably larger from the single seven-ounce dose than the total of seven one-ounce doses.

Further study needs to be done with the macaque model to determine whether PPEC or relative exposure is a better predictor of prenatal effects. In the meantime, the results of this study suggest that human epidemiological studies may benefit from focusing attention on models that measure total fetal exposure rather than average daily exposures.

We anticipate teratogenic outcomes from in utero ethanol exposure in the liveborn macaques. These problems may not be found to occur at the same exposures as those related to fetal loss. We shall report the outcome of the liveborn infants' development, phenotype, and anatomy as the data analyses are completed.

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Physical Anomalies and Developmental Delays in Nonhuman Primate Infants Exposed to Weekly Doses of Ethanol During Gestation

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ABSTRACT Ethanol was orally administered once per week to 54 gravid pigtailed macaques (*Macaca nemestrina*) in doses of 0.0, 0.3, 0.6, 1.2, 1.8, 2.5 or 4.1 gm/kg from the 1st week in gestation or in doses of 2.5, 3.3, or 4.1 gm/kg from the 5th week. Mean maternal mean peak plasma ethanol concentrations (MPPEC) ranged from 24 ± 6 mg/dl at the 0.3 gm/kg dose to 549 ± 71 mg/dl at the 4.1 gm/kg dose. Thirty-three viable infants were followed from birth to 6 months of age and assessed for growth, health, congenital anomalies and developmental rate. Facial anomalies, growth deficiency, or central nervous system dysfunction were found in 57% of the alcohol-exposed animals. No animal showed all the features of the human fetal alcohol syndrome. Ten of the twelve animals (83%) with mean MPPEC above 140 mg/dl had evidence of a teratogenic impact. The animals with full gestational exposure to ethanol and mean MPPEC between 140 and 249 mg/dl had much more severe and consistent cognitive abnormalities than the animals with delayed gestational exposures, even though the latter were exposed to mean MPPEC between 260 and 540 mg/dl. Conclusions from this study included: 1) ethanol-related behavioral teratogenesis occurred without accompanying physical anomalies, 2) measurable teratogenic effects from *weekly* exposures occurred only at intoxicating doses of ethanol, and 3) early gestational exposure to ethanol appeared to be more damaging to cognitive function than later and considerably greater alcohol exposure.

Central nervous system dysfunction is the most frequent and most severe teratogenic result of intrauterine ethanol exposure (Clarren and Smith, '78). Decreased cognitive ability, distractibility, and hyperactivity have all been frequently observed in children with fetal alcohol syndrome. Intellectual deficits without structural birth defects in other organ systems are observed more frequently in children exposed to ethanol during gestation than in those not exposed (Streissguth et al., '84). Extensive studies in animals, especially rats, confirm the behavioral teratogenicity of ethanol (Bond, '86; Riley et al., '86). There is little useful information available yet, however, concerning the fetal margins of safety in ethanol dosage or exposure pattern. In humans, this lack of information stems from problems in inaccurate reporting of exposure, marked variability in individual drinking patterns leading to artificial averaging of exposures, and difficulty in confident detection of behavioral fetal alcohol effects. Dose-response extrapolation from rodents to humans becomes problematic because small laboratory animals metabolize ethanol differently than primates, have less prenatal brain development, and have a

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lower cognitive potential. This study was undertaken as a first step in correlating developmental dysfunction and gestational ethanol exposure in a nonhuman primate (*M. nemestrina*) using a once per week exposure model.

METHODS

A total of 33 liveborn infant macaques were assessed in this project. The methods of managing their pregnancies have been fully reported previously (Clarren et al., '87). Initially it had been planned that each infant would be exposed to ethanol once weekly from the 1st week after its conception until birth about 24 wk later. Dosing was performed on all animals on the same day of the week at 9 A.M. following a 16 hr fast. Maternal dose cohorts were established with ethanol exposures of 0.0, 0.3, 0.6, 1.2, 1.8, 2.5, 3.3, and 4.1 gm/kg. Ethanol was diluted by volume in four parts water and administered via a soft nasogastric catheter. (The 0.0 animals received a sucrose solution that was isocaloric and isovolemic to the highest dose of ethanol and delivered in the same manner.) The dams' plasma ethanol disposition curves were determined in each trimester as previously described (Clarren et al., '87). The mean maternal peak plasma ethanol concentration (MPPEC) of each mother was derived from the three determinations in each animal.

As the study progressed, it became clear that ethanol exposures administered from the 1st week in gestation in doses of 2.5 gm/kg or more (MPPEC 250 mg/dl) were sufficiently toxic so as to preclude an adequate number of viable infant subjects. Consequently, a two-group study was developed: animals dosed at the 1.8 gm/kg level and below received weekly doses from the beginning of pregnancy (subsequently referred to as the full gestation exposure group, or FGE), and animals receiving the 2.5 gm/kg dose or more received their 1st weekly ethanol dose 33 to 46 days postconception (delayed gestation exposure group, or DGE).

Three weeks prior to an expected delivery date, the pregnant dam was transferred to the maternity suite of the Infant Primate Research Laboratory. The maternity suite was a 24 hr care facility where pregnancy and labor were monitored each one-half hour, around the clock, via closed circuit television using an infrared camera to avoid disrupting the animals' normal light/dark cycle. When labor was observed, the obstetrical team was summoned. After the infant was delivered, the mother was sedated with an intramuscular injection of ketamine (10 mg/kg), and the infant and placenta were removed, weighed and examined.

When an infant was to be delivered by caesarian section, the dam was removed to the operating room prior to onset of labor and the procedure was performed under halothane anesthesia by a staff veterinarian. The procedure took approximately 30 min.

Among the FGE animals, 22 had normal, spontaneous vaginal deliveries while five required caesarian section because of persistent fetal breech position or prolonged pregnancy. For five of the six DGE infants, caesarian sections were conducted as a matter of protocol at about 160 days gestation, slightly earlier than a mean term gestation, in order to minimize the risk of perinatal loss in this high exposure and potentially higher risk group. Since the DGE animals were born slightly earlier than the other infants, all test outcomes that were measured as age to criterion were analyzed both in terms of postconceptional age and postnatal age.

The newborn infant exam included ascertaining the simian Apgar score 5 and 10 min following delivery. Assessments included in the Apgar score were the respiratory rate, heart rate, muscle tone, behavioral state, skin coloration, and rectal temperature. These scores were solely used for neonatal monitoring since they were influenced by the maternal sedation. Additionally, the infants were assessed for rooting, sucking, grasping, eyeblink, and righting reflexes. Birthweight was recorded and the infant was placed in an isolette under 24 hr care in the newborn suite. All subsequent testing was done by examiners blind to the gestational ethanol exposures.

The morning after delivery, a more thorough physical examination of the infant was performed. Specific observations included body proportions, pigmentation, head molding, fontanelle size, overriding sutures, facial symmetry, and tooth eruption. Thereafter the animals were weighed and measured at regular intervals. Health was assessed daily. Food intake, sudden changes in weight, diarrhea, or other signs of ill

health were noted. In addition, the infants were carefully scrutinized for major and minor anomalies by a dysmorphologist (SKC).

Computerized medical records were maintained on each infant by the full-time veterinary staff and included information on gestation, body weight, housing, hematology, blood chemistry, and virology.

The feeding schedule for each infant proceeded from a 50% human formula (SMA, Wyeth Laboratories, Philadelphia, PA) and water in a hand-held bottle through a series of self-feeding challenges to total weaning at about 17 postnatal wk. The housing schedule proceeded from isolette through temperature regulation challenges to housing in an individual cage in a large general infant housing suite. The animals were housed with parental surrogates (diapers) until 140 postnatal days of age, and had a daily social experience with groups of like-aged peers in the playroom.

Postnatal growth was followed by obtaining specific anthropometric measures at birth 173, 187, 215, 243, 271, 299 and 355 days after conception (typical gestation being 160 ± 12 days) (Sackett et al., '75). The measures included left foot and crown-rump length, head length and width and head circumference, which was measured above the ears and below the supraorbital ridge. Two independent measures were recorded to the nearest millimeter for each parameter and the mean value used for analysis. At 1 and 6 months of age, standard frontal and lateral cephalometric radiographs and photographs were obtained.

Six infant developmental/behavioral measures were employed. Assessments requiring subjective ranking of behavior and/or performance were conducted by testers for whom inter- and intra-observer reliability was high. All testers were blind to the infants' cohort status.

Neonatal reflex assessments included noting resistance to passive movement of limbs, the strength of grasping, and rooting, sucking, and snouting reflexes; observing the infant's auditory startle response, visual orientation and tracking, the onset of species-specific facial expressions; testing the leg and arm placing reflex, and the clasping and righting reflexes. Each measure was recorded on a six-point ordinal scale. Each exam took approximately 10 min and was performed every other day from birth to 2 wk of age (Infant Primate Research Laboratory, '86; Mowbray and Cadell, '62).

Nutritive sucking capability was measured using a procedure developed by Kron et al. ('63) which has been successfully applied to macaque neonates by Burbacher ('83). Each infant was tested daily from birth through 9 days of age using an apparatus that consisted of a graduated cylinder filled with nutritive liquid. The cylinder was attached through capillary tubing to a nipple that could deliver a consistent flow of the liquid at a constant pressure. Pressure changes were measured by a pressure transducer which was attached to the tubing and connected to a four-channel polygraph. Measures included the age when the infant was first able to suck, the total number of sucks per session, and mean length, amplitude and velocity of each suck.

The *object permanence assessment* documented the development of object permanence conceptualization in the infant macaque from 2 to 16 wk (Redshaw, '78; Williams, '79). The assessment, based on the procedure developed by Piaget for human infants (Flavell, '77), was as follows:

At 2 wk of age, the infant was held by one tester as a second tester presented the infant with one of four tasks. The first task required the infant to reach and grasp an object within plain view. The second and third tasks required the infant to locate and retrieve an object partially and fully hidden from view behind a screen and within a small well. The fourth task required the infant to locate the object placed in one of two covered wells. In all cases, the infant watched the tester hide the object. The infant was allowed 15 sec to respond to each trial. The infant had to reach criterion in task one prior to advancing to the second and third tasks, which were run simultaneously. Criterion had to be reached on both tasks two and three prior to advancement to task four. Testing was performed twice weekly and was scored in three ways: postconceptional age, postnatal age and the number of test sessions to criterion.

The *Wisconsin General Testing Apparatus* (WGTA) was used to measure early infant learning strategies (Harlow, '59). The WGTA was administered 5 days per wk between 4 and 6 months of age postnatally. It provided a measure of an infant's ability to form a systematic pattern of responses

while searching for a reward hidden under colored blocks or within boxes. The infant was placed in a special cage which allowed him access to the testing apparatus without viewing the tester. An opaque barrier prevented the infant from observing stimulus changes between trials. The tester could view the infant through a one-way mirror. The WGTA assessment was comprised of nine individually scored tasks. The infant was adapted to the task of retrieving an apple bit from a food well covered by a small yellow block. Adaptation progressed in three stages as the infant learned to retrieve the apple bit from an uncovered well, a half-covered well and finally, a well completely covered by the yellow block. Upon adaptation, the infant progressed to black/white discrimination. The infant was presented with two blocks, one black and one white, each covering a food well. The infant first had to learn that the reward was always under the black block and then reverse his pattern and learn to retrieve it from under the white block.

Upon mastering this task, the infant proceeded to Hamilton Search activities. Prior to testing, the infant was adapted to the task of retrieving an apple bit from a small box with a hinged lid in three stages: retrieving the bit from an open box, a half-closed box and a fully closed box. Each day the infant was presented with a task and given 25 opportunities to respond to the task. Each response had to be made within 3 min and the infant needed to reach specific criterion on each task before advancing to the next. First, the infant was presented with four closed green boxes arranged in a single row and he or she had to develop an efficient search pattern to locate and retrieve an apple bit that was randomly allocated to one of the four boxes. Next, the apple bit was placed in the box which had been selected least often by the infant and the process of 125 trials was repeated, only this time the infant was allowed to open as many boxes as was necessary to locate the reward. Finally, the infant located the reward which was again placed in the same least-favored box, but this time he or she was only allowed to open one box to locate the reward. Scores were recorded as postnatal age and number of test sessions to criterion. Response latency for each trial was also recorded.

Visual recognition memory was developed as an early measure of intelligence (Fagen, '77). Visual recognition is measured by differential fixation to novel over familiar two-dimensional abstract patterns. Preferential fixation on a novel pattern demonstrates that an infant can distinguish between two patterns and can remember a pattern previously seen. It has been hypothesized that human and nonhuman primates at risk for cognitive deficits direct less visual attention to novel stimuli than control subjects (Gunderson et al., '86). An adaptation of Fagan's novelty paradigm (Fagan, '70) was administered to the infants in this study at 190, 200 and 210 days postconception. Prior to administration of this assessment, visual acuity was examined on all infants and found to be within normal bounds. The visual stimuli used in the novelty paradigm were high-contrast, black and white, abstract patterns. Different patterns were presented to the infant at each test session. The test patterns were back-projected onto a display board through two 9 cm square screens. The tester, holding the infant 36 cm from the stimuli, viewed the animal's face via a video monitor and recorded fixations to the right and left using timers operated by foot pedals. The tester was blind to the animal's exposure and to the stimuli presented on the screen. The infant was first presented with two identical patterns and was required to fixate on them for an accumulation of 60 sec. The animal was then presented with a two-part test trial in which the previously exposed pattern was paired with a novel one. Looking time to each pattern was recorded for 10–20 sec depending on the trial. The position of the two patterns were reversed, to control for side preferences. Looking time was recorded once again for 10–20 sec. The test was scored by comparing the proportion of time the infant looked at the novel vs. the familiar pattern. An alternate method of scoring this test was to compare the amount of time the subject looked at both images vs. neither image, in which case time spent looking away from the targets may be a measure of distractability. We evaluated the subjects both ways.

Playroom motor and behavioral observations began at 15 days of age. The infants were entered into social groups of five or six age-matched peers from the infant colony and placed in an observation playroom for 30 min of daily social interaction. The room

contained shelves at various levels, a ramp, a suspended rope and toys. Motor, postural and special communication behaviors involving the abilities to sit, stand, walk, climb and display various postures and facial expressions were observed in response to other monkeys and to various appartus in the playroom (Sackett et al., '76). The age of onset of 12 motor behaviors and three facial expressions were recorded during 5–min observation periods that occurred twice weekly on each infant. Some of the measures recorded in the playroom were continuations of Neonatal Assessments measures that were observed weekly on each infant. The playroom assessments continued until the infant reached 6 months of age.

Data analysis for each assessment was approached in two ways. First, dose-response relationships between the independent variable MPPEC and the numerous dependent variables including gestational length, growth parameters (weight, height, head circumference) and the scores of each measure on the six developmental tests were analyzed by linear regression. All variables were measured on continuous scales. In addition, comparison of dose cohort means for each dependent variable were performed with one-way ANOVA. This approach, however, could only identify very robust effects in the data set; since the power of the tests was limited by the small group sizes (dose-cohort N's = 4–6). Consequently, a second approach was employed which identified individual animals with delayed performance for each dependent variable. Delayed individuals were detected by transforming each infant's raw score into a normally standardized z score. Delayed individuals were defined as those infants with measured scores greater than 2.57 standard deviations (corresponding to a 99% confidence interval) from the overall mean of the unexposed infants. The tests were scored and the decision made to define an animal as delayed without knowledge of subject exposure. Some individual animals were found to be significantly delayed on nearly every measure.

RESULTS

Figure 1 summarizes all abnormalities of growth, morphology, health, and development as described in the paragraphs below.

Fetal growth and duration of gestation

Animal 33 was the only growth retarded animal and the only liveborn infant in the 4.1 gm/kg DGE dose group (MPPEC = 539 mg/dl). When compared to all exposed and non-exposed male infants in the study, animal 33 had the lowest prenatal and postnatal growth rates and the lowest birthweight. Its postnatal weight gain profile paralleled the age and sex matched growth curve for the colony but measured 160 gm below the curve. Furthermore, animal 33 was the only microcephalic infant in the sample with a head circumference below the 99% confidence interval at birth and at 6 months. The microcephaly was proportionate to body weight. There was no detectable relation-

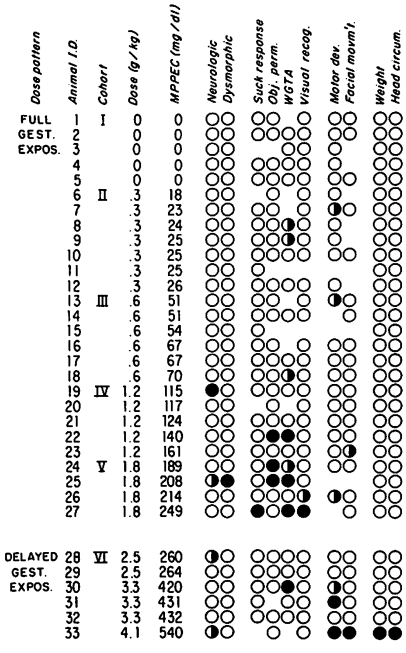

Fig. 1. Individual deviations on developmental and growth measures are compared in infant macaques exposed to ethanol in utero. ● indicates extreme deviations from control means, while ◑ indicates definite but less extreme deviations. Definitions for deviations in each column are found under "Results." Absent circles indicate missing or incomplete data.

TABLE 1. Minor dysmorphic features in animals exposed to alcohol once per week in gestation

Dose group	Animal	Mean MPPEC[1]	Dysmorphia
FGE	12	26	Ptosis
FGE	13	51	Floppy ears
FGE	21	124	Dental anomalies (upper incisors)
FGE	25	208	Flattened philtrum Dental anomalies (upper incisors) Flattened maxilla
DGE	32	432	Unusual auricles Metopic synostosis

[1]MPPEC = maternal peak plasma ethanol concentration.

ship between birth weight, birth length or head circumference and ethanol exposure among the other 32 animals.

A linear regression analysis of postconceptional age for tooth eruption demonstrated a significant dose response for early eruption of each of the four canines with increasing ethanol exposure through the FGE and DGE groups. Ethanol exposure explained 19–24% of the variance in the timing of eruption of each canine (all four *P*-values were $< .01$). The dental eruption was accelerated by 2 to 8 wk relative to controls. Other primary teeth did not show this precocity.

There was no association between duration of gestation and ethanol dose in non-c-sectioned FGE animals. Since most DGE animals were delivered by c-section at the same post-conceptional age of 160 days, it was not possible to relate exposure to their gestational duration except to say that it was in no case more than 8 days shorter than the average 168 days for animals in this study.

Congenital anomalies

No control animals had any major or minor dysmorphic features. Three FGE infants exposed to low or moderately high ethanol doses (MPPEC between 26 and 124 mg/dl) had an isolated minor anomaly (Table 1). Animal 25 (MPPEC of 208 mg/dl) had a cluster of three minor anomalies that have been typically observed in humans with fetal alcohol syndrome. One of the six DGE animals had two minor malformations that were not considered typical of ethanol teratogenesis in humans. No major malformations other than the microcephaly in animal 33 were observed in any animal, nor was a consistent pattern of minor dysmorphic features of the face or overall phenotype discerned.

Health

Three infants developed serious infectious illnesses. At 12 days of age, animal 11 (MPPEC = 25 mg/dl) developed overwhelming septicemia from coxsackie enterovirus, pseudomonas, and staphylococcus aureaus and died at 23 days of age. Animal 12 (MPPEC = 26 mg/dl) and animal 15 (MPPEC = 54 mg/dl) developed chronic diarrhea. Animal 12 survived while animal 15 expired. Infectious illnesses, especially diarrheal illnesses, are common among colony infants, but generally these illnesses are brief and self-limited. No explanation of underlying conditions which might have precipitated these deaths was found at autopsy. Immunologic studies for simean acquired immune deficiency were not being routinely obtained at the time these infants expired.

Animal 19 (MPPEC = 115 mg/dl) had four brief grand mal seizures between 115 and 133 days of life without metabolic or infectious etiology (noted on Fig. 1 as ● in the neurologic abnormality column). Three animals (25, 28 and 33) had strabismus which resolved spontaneously over several months (noted by ◑ on Fig. 1 in the neurologic abnormality column).

Development

No substantial individual deviation was found for any animal among the *neonatal reflex* assessments. All animals began to suck in the test of *nutritive sucking* on the 1st or 2nd day of life except for animal 27, who did not suck until the 5th day ($z = 2.87$) (denoted by ● in Fig. 1). This result was not associated with gestational length below the mean (168 days), nor was it associated with c-section delivery.

The *object permanence* test was scored using postnatal and postconceptional age to

criterion and number of test sessions to reach criterion. Three animals (22, 24, and 25) had consistant significant delays by all three scoring systems and these were denoted by ● in Fig. 1.

Four animals (8, 9, 18, and 24) were significantly delayed on *WGTA* in completing one or two tasks but still completed the entire set of nine tasks prior to the end of the study (denoted in Fig. 1 by ◑). Four animals (21, 25, 27, and 30) were so delayed on the initial *WGTA* tasks that they never completed the battery by the study's conclusion and were hence very significantly deviated (denoted by ● in Fig. 1).

The initial tasks of WGTA are tests of performance while the later tasks assess associative learning. The pattern of difficulty found in all eight abnormal monkeys clearly demonstrated performance difficulties. While associated learning was mildly impaired in four animals it was not tested in the other four who never reached those assessments under the confines of the testing protocol.

When the *visual recognition* test was scored in the usual manner, no animals were found to be aberrant. When the test was assessed as a measure of distractibility, two animals, 26 and 27, stood out as spending excessive time looking away from the targets, varying by more than 2.56 standard deviations from the mean of control animals for times looking away. Animal 27 was the more aberrant of the two (denoted by ● in Fig. 1, while ◑ was given to animal 26).

Among the five measures of *motor function* observed in the playroom only six animals were delayed beyond the 99% confidence interval on one or more tasks. Animals 7, 13, 26 and 30 failed one or two items (◑), while animals 31 and 33 were very deviant, failing four and five tasks respectively (denoted by ●). There were six measures of *facial movements*. One animal, 23, had significant delay on one item (denoted by ◑), and animal 33 had more than three significant delays (●).

DISCUSSION

This study was undertaken to determine the fetal effects of weekly exposure to alcohol, the most common frequent intermittent consumption pattern among American women (Wilsnack et al., '84). Our goal was to obtain data that would correlate dose with specific dysfunctional outcomes of ethanol teratogenesis.

No animal in this study showed all the features of the human fetal alcohol syndrome although facial dysmorphia, growth deficiency and central nervous system dysfunction were all found in 16 of the 28 alcohol-exposed animals. Perhaps the most significant result was the consistency with which FGE animals with MPPEC > 140 mg/dl demonstrated developmental delays, while DGE animals—who were exposed to much higher levels of ethanol after gestational wk 5—were more cognitively intact at 6 months of age.

Among the FGE animals, physical abnormalities included seizures in animal 19 (MPPEC = 115 mg/dl) and significant facial dysmorphogenesis in animal 25 (MPPEC = 208 mg/dl). Spontaneous seizures are very rare in infants in our colony: between 1983 and 1986 only five of 667 (0.7%) macaques had unexplained seizures. The chance occurrence of one infant in 33 having seizures would be 12%. Chernick has described EEG changes as a frequent observation in human infants exposed to moderate and high dose ethanol in utero (Chernick et al., '83). Whether seizures are related to ethanol teratogenesis in this model will require further study.

Animal 25's minor facial anomalies occurred in the premaxillary and philtral regions, a facial zone sensitive to ethanol teratogenesis in humans and in mice. No specific time in gestation has been related to facial alterations in human FAS. Sulik ('84) has demonstrated alteration in this facial zone in mice exposed to ethanol on day 7 of gestation. Newell-Morris and co-authors demonstrated that maxillary and branchial anomalies of the face occurred in the pigtailed macaque exposed to retinoic acid between 20 and 44 days of gestation (Newell-Morris et al., '80). Assuming that ethanol altered the face in roughly the same time period of gestation as retinoic acid, and given that the DGE animals received ethanol from day 33 in gestation without impact to facial form, the period of facial teratogenesis for alcohol would be between gestational days 20 to 32. Animal 25 was exposed to ethanol on days 24 and 31 within this apparent period of vulnerability for facial alteration and was the only FGE animal in the 1.2 or 1.8 gm/kg cohorts exposed to ethanol on those particular days. Further

studies will test the specificity of these days in gestation to facial alteration in the macaque.

All animals with MPPECs above 140 mg/dl in the FGE group were identified as developmentally delayed in some way. Eight of the nine "definitely delayed" scores on the nutritive sucking capability test, object permanence assessment, WGTA, and visual recognition memory assessment occurred in four of these animals. These animals did not demonstrate significant delays in motor and social development as observed in the playroom. Only one of the animals had facial dysmorphia, a finding which strengthens the clinical opinion that human infants gestationally exposed to alcohol may have a behavioral teratogenic effect without a facial anomaly.

The DGE group included the only growth-retarded and microcephalic animal (33) with a MPPEC of 539 mg/dl. Similar retardation in brain growth had been previously reported in an infant macaque exposed to this same dose and dosing schedule (Clarren and Bowden, '82). Decreased body fat is an important component of the growth deficiency in human children with fetal alcohol syndrome (Clarren and Smith, '78). Normal macaque infants have only 2% body fat at term (Newell-Morris and Fahrenbruch, '85) as compared to 15% body fat in term gestation humans (Widdowson, '81) and this may explain why weight deficiency was only seen in very high ethanol exposures in this study.

Two of the three infants with transient strabismus occurred in the DGE group. This form of strabismus has been observed to occur in 4% of macaques infants in our colony (Kiorpes et al., '85). Our three affected infants represent 9% of all study infants or 33% of the DGE infants. The chance occurrance for strabismus in 3 of 33 infants would be 10%. High dose exposure after the 5th wk in gestation may increase the rate of strabismus, but further study will be needed to confirm this observation.

Two factors that could have potentially confounded the behavioral effects of ethanol teratogenesis were caesarian-section delivery and shorter gestational duration. Both factors were present in five of the six DGE infants as a consequence, of elective c-section delivery at 160 days' gestation to circumvent possible perinatal loss in this high risk group. These factors were much less extensive in the FGE group. Neither factor confounded associations of ethanol exposure to developmental delay.

Acceleration in the development of the canine teeth was found as a cohort-related effect independent of FGE/DGE designation. Accelerated tooth eruption has been reported in children exposed in utero to maternal smoking (Rantakallio and Makimen, '83) and in rats with prenatal exposure to methyl mercury (Vorhees, '85; Geyer et al., '85). Early dental eruption has not been previously described with ethanol teratogenesis, but delayed dental eruption has been observed after gestational ethanol exposure (Kelly et al., '87, Vorhees and Fernandez, '86). When a more complete understanding of the determinants of tooth eruption are known and the actions of alcohol upon that system are understood, then perhaps these apparent contradictory results can be reconciled.

In a previous article, we reported that spontaneous abortions in this model were related to ethanol exposures at and above mean MPPEC's of 200 mg/dl (Clarren et al., '87). The data reported here suggest that developmental dysfunction becomes measurable in early infancy with ethanol exposure at and above MPPEC's of 140 mg/dl. Such blood alcohol levels would be achieved in women of average weight (55 kg) consuming approximately 2.5 to 3.0 ounces of ethanol at one time once per week. The data should not be interpreted to mean that weekly dose exposures below 140 mg/dl ethanol are necessarily safe. Marginal developmental delays were identified in the playroom observations and on the WGTA in animals in all of the ethanol exposed cohorts. In addition, cognitive losses might not emerge until the animals were older and beyond the age limits of this study.

This study suggests that very early gestation may be a time when brain tissues are especially vulnerable to alcohol. Generally speaking, women do not suspect they are pregnant within the first month of gestation and may continue a pre-pregnancy drinking pattern that they would not choose to keep while pregnant. Thus, the implications from our study regarding the relationship of early gestational ethanol exposure to cognitive delays are disquieting. Further studies to determine whether detrimental effects of early exposure can be reversed by abstinence in later gestation have been initiated.

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Morphometric Analysis of *Macaca nemestrina* Exposed to Ethanol During Gestation

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ABSTRACT This study was part of a multidisciplinary investigation of the effects of gestational ethanol exposure in nonhuman primates. Thirty-one pregnant *Macaca nemestrina* were exposed to weekly ethanol doses of 0.0, 0.3, 0.6, 1.2, 1.8, 2.5, 3.3, or 4.1 g/kg maternal weight. Dose cohorts 0.0 through 1.8 were exposed to the initial ethanol dose within 10 days postconception. Dose cohorts 2.5 through 4.1 received their initial dose after the fifth week of gestation. Morphometric analyses performed on cranial radiographs showed that animals exposed to high doses of gestational ethanol had, on average, slightly smaller, distorted crania than control animals. A dysmorphic, flat face characteristic of fetal alcohol syndrome was recognized in one animal of the 1.8 g/kg cohort. The animal that received the highest doses of gestational ethanol was microcephalic. Similar malformations were not seen with low ethanol exposures or in controls. These data suggest a pattern of cranial distortion that may be recognizable and characteristic of ethanol teratogenesis.

Fetal alcohol syndrome (FAS) is a pattern of malformation produced by gestational exposure to ethanol and is defined by: central nervous system dysfunction, growth deficiency, and a specific cluster of minor facial anomalies (Clarren and Smith, '78). Since growth and developmental delays are found in numerous birth defect syndromes, the specific cluster of minor facial anomalies is important in distinguishing FAS. The fact that facial anomalies have been recognized as causally related to prenatal ethanol exposure has given rise to speculation about the mechanism of teratogenesis, and the threshold and spectrum of ethanol teratogenesis at different gestational ages.

This study of facial form in nonhuman primates was part of a multidisciplinary investigation of gestational ethanol exposure. The methods of alcohol administration, handling of the pregnancies, pregnancy outcome results, overall physical condition, and cognitive and developmental performance of the infants have been detailed in previous reports (Clarren et al., '87b, '88). The purpose of the morphometric investigation was to use radiographs to characterize the crania and facial features of control animals and compare them with the features of animals exposed to ethanol during gestation.

MATERIALS AND METHODS

The 31 *Macaca nemestrina* used in this study were exposed prenatally to weekly doses of ethanol. The maternal oral ethanol dose assignments were 0.0, 0.3, 0.6, 1.2, 1.8, 2.5, 3.3, and 4.1 g/kg maternal weight. Those animals assigned to dose cohorts 1.8 g/kg and below received their initial weekly dose within 10 days after conception (referred to as "full gestational exposure" or "FGE"). Animals assigned to cohorts 2.5 through 4.1 g/kg received their initial

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TABLE 1. Distribution of the sample

	Maternal ethanol cohort								
	C[1]	C	1	2	3	4	5	6	7
Number of males	7	2	3	3	3	3	1	1	1
Number of females	8	3	3	2	2	1	1	2	0
Total subjects	15	5	6	5	5	4	2	3	1
Weekly maternal ethanol dose (g/kg)	0.0	0.0	0.3	0.6	1.2	1.8	2.5[2]	3.3[2]	4.1[2]
Cohort mean maternal peak plasma ethanol concentration (mg%)	0	0	23	61	131	215	262	427	539

[1]Control subjects from mothers who were not gavage fed glucose during gestation.
[2]Subjects received their initial ethanol exposure between 33 and 46 postconceptional days.

weekly dose between 33 and 46 days postconception (referred to as "delayed gestational exposure" or "DGE").

Standardized lateral cephalometric radiographs of their progeny were taken with the anesthetized animal seated in a cephalostat designed for nonhuman primate research. Lateral radiographs were taken at age 1 ($\bar{x}$ = 221 postconceptional days, range 195–281 postconceptional days), and at age 2 ($\bar{x}$ = 337 postconceptional days, range 285–370 postconceptional days). Frontal radiographs were made after sacrifice, with the preserved specimen heads oriented to a standard plane in the cephalostat. Age at sacrifice ranged from 330 to 381 postconceptional days, with a mean of 356 postconceptional days.

Fifteen additional sex- and age-matched control *M. nemestrina* were obtained from the primate breeding colony that had been the source for the ethanol cohort sample. Criteria for selection included: no intra- or extrauterine exposures to conditions or medicaments that might adversely affect craniofacial growth and ages comparable with those of animals in the cohort sample. These additional control animals had lateral cephalometric radiographs taken that were identical to the fetal ethanol cohort sample.

Table 1 illustrates the distribution of the sample. Each animal's identification number, sex, dose cohort, maternal peak plasma ethanol concentration (MPPEC), and postconceptional age for lateral and frontal radiographs are recorded for each animal included in this project in Table 2.

Identification of landmarks used for digitization was done with a magnifying glass to inspect radiographs illuminated on a viewbox in a dark room. The coordinates of the landmarks were recorded using a digitizing tablet and microcomputer. Figures 1 and 2 illustrate and define the landmark points used in the analyses.

The digitized points were analyzed using morphometric methods developed by Bookstein ('86). The methods quantify mean differences in cranial or facial shape, which may distinguish the experimental group from a control group. Data generated in a study of facial features of humans with FAS have been similarly analyzed with these methods, as introduced by Bookstein ('86).

Landmark analysis was carried out primarily in terms of triangles defined by sets of three landmark points. One edge of each triangle was arbitrarily selected and assigned a standard length with the point coordinates (0,0) and (1,0) in a Cartesian (x,y) system. All information about the shape of the triangle was contained in the relative x,y coordinates of the third point, the shape coordinates (Fig. 3A).

After standardizing a triangle, such as Bregma-Orbitale-Lambda, in the manner described above, shapes were plotted as an x,y scatterplot of the shape coordinates (Fig. 3B). The mean shape for a group of triangles is represented by the average value of its scatter of shape coordinates. The significance of the observed difference in mean shape between ethanol-exposed and unexposed groups was assessed using Hotelling's two-sample T^2 test applied to the bivariate shape coordinate data (Clarren et al., '87a). Multiple triangles describing cranial and facial shape were examined.

Some individual comparisons were made by superimpositions of outlines of the anterior cranial base anatomy. The anterior wall of the sella turcica, anterior contours of the middle cranial fossae, contours of the cribiform plate and the frontoethmoidal crest, and the cerebral surface of the orbital roofs were aligned by eye to achieve the best possible fit. These reference structures are commonly used in orthodontic diagnosis and research, as they are located outside of the face itself (Bjork, '60; Bjork and Skieller, '83).

TABLE 2. Subject number, sex, maternal ethanol cohort, maternal mean peak plasma ethanol concentration, and age at times of radiographs

Subject number	Sex	Maternal weekly ethanol dose (g/kg)	Mean maternal peak plasma ethanol (mg%)	Postconceptional age		
				Lateral X-ray 1	Lateral X-ray 2	Frontal X-ray
1	F	0.0	0	219	354	359
2	F	0.0	0	202	322	352
3	F	0.0	0	280	338	381
4	M	0.0	0	242	341	346
5	M	0.0	0	206	332	347
6	M	0.3	18	214	319	330
7	F	0.3	23	213	327	345
8	F	0.3	24	200	354	363
9	M	0.3	24	215	348	367
10	M	0.3	25	229	348	374
11	F	0.3	25	201	370	370
13	F	0.6	51	205	350	350
14	M	0.6	51	203	301	358
15	M	0.6	67	236	326	338
16	M	0.6	67	222	360	363
17	F	0.6	70	225	360	380
19	F	1.2	115	221	342	363
20	F	1.2	117	235	359	359
21	M	1.2	124	281	360	360
22	M	1.2	140	235	353	361
23	M	1.2	161	201	318	348
24	M	1.8	189	228	326	350
25	F	1.8	208	218	352	358
26	M	1.8	214	224	340	354
27	M	1.8	248	210	352	358
28	M	2.5[1]	260	206	324	355
29	F	2.5[1]	264	202	343	350
30	F	3.3[1]	419	199	330	338
31	M	3.3[1]	431	195	328	348
32	F	3.3[1]	432	210	331	344
33	M	4.1[1]	539	254	326	362
34	M	0.0	0	249	—	—
35	M	0.0	0	251	—	—
36	F	0.0	0	214	—	—
37	F	0.0	0	227	—	—
38	F	0.0	0	244	—	—
39	M	0.0	0	—	366	—
40	M	0.0	0	—	342	—
41	M	0.0	0	—	298	—
42	M	0.0	0	—	338	—
43	M	0.0	0	—	324	—
44	F	0.0	0	—	285	—
45	F	0.0	0	—	370	—
46	F	0.0	0	—	373	—
47	F	0.0	0	—	295	—

[1]Subjects received their initial ethanol exposure between 33 and 46 days postconception.
—, Data not collected.

The amount of facial and cranial growth for an individual may be evaluated by superimposing cephalometric tracings made from radiographs taken at different points in time (Ghafari et al., '87). Tracings of two age- and sex-matched subjects superimposed on the anterior cranial base have been used to qualitatively describe facial and calvarial shape differences between the subjects (Inouye et al., '85).

RESULTS

One FGE animal (no. 25) in the 1.8-g/kg cohort (MPPEC = 208 mg%) was dysmorphic, with a flat philtrum and a flattened midface (Clarren et al., '88). The facial shape coordinates of this animal did not differ statistically from the control group. However, superimposition of the radiographic tracing of animal 25 with an age- which facial characteristics contributed to

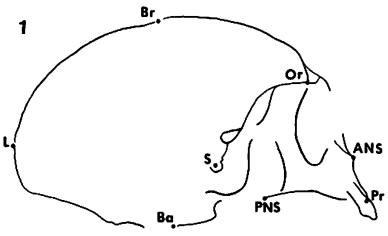

Fig. 1. Landmarks on lateral radiographs. Br, bregma, point at junction of coronal and sagittal sutures; Or, orbitale, junction of orbital roof and inner table of the frontal bone; S, sella, center of the sella turcica; ANS, anterior nasal spine; Pr, prosthion, most anterior, inferior point on premaxilla; PNS, posterior nasal spine; Ba, basion, most anterior point of foramen magnum; L, lambda, most superior point on lambdoid suture.

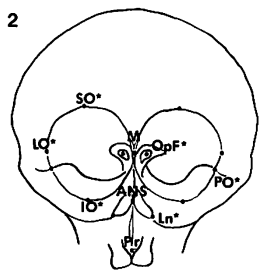

Fig. 2. Landmarks on frontal radiographs. *Bilateral points. SO*, most superior portions of orbital rim; LO*, most lateral portion of orbital rim; PO*, intersection of petrous portion of temporal bone and lateral orbital rim; OpF, center of optic foramen; M, intersection of medial portion of orbits with cribiform plate; IO*, most inferior portion of orbital rim; ANS, anterior nasal spine; LN*, most lateral portion of nasal cavity; Pr, most anterior, inferior point on premaxilla.

the clinical impression of dysmorphic features (Fig. 4). This animal had a dose schedule unique in the cohort; the dosing began on the third postconceptional day, with subsequent weekly doses.

Another animal exhibited microcephaly. This animal (no. 33) was a member of the delayed gestational exposure cohort and was exposed to the highest levels of ethanol in this study (MPPEC = 539 mg%). The head circumference was below the 99th percentile for the species at birth and at 6 months (Sackett et al., '75). The facial structure did not appear abnormal on examination of superimposed radiographic outlines or in terms of facial shape coordinates (Fig. 5).

Comparison of all ethanol-exposed specimens with the controls revealed no statistically significant differences in shape between the groups. Comparison of controls with individual FGE cohorts and with a cohort composed of all DGE animals yielded no significant findings. The small number of subjects in each cohort restricted the power of statistical tests. In subsequent analyses, the four highest FGE (1.8 g/kg) and the six DGE (2.5, 3.3, 4.1 g/kg) subjects were compared with a group combining the 16 low-ethanol exposure subjects with the 20 control animals.

Lateral analysis

There were no clearly significant relationships between facial shape coordinates and classification by ethanol exposure at either age. There was a difference in cranial shape, however, defined by the triangles within the quadrilateral Br-Or-S-L (Table 3). The mean cross-sectional area of Br-Or-S-L was approximately 3.5% smaller in high-dose animals (Table 4). The mean difference was statistically significant ($P \leq 0.04$, one-sided test) on the basis of a random effects regression analysis of log (area) appropriate for longitudinal data, which took into account each subject's sex, age at the times of radiography, degree of ethanol exposure, and the fact that most subjects had data collected at two ages while others were observed only once (Laird and Ware, '82). Figure 6 interprets this mean distortion in cranial shape with respect to approximate registration on Or-S. Mean two-dimensional cranial area in the high-dose animals was reduced by 1.7% compared with controls.

Frontal analysis

Morphometric analysis of multiple triangles describing facial shape and features in the frontal plane revealed no significant alteration of frontal facial features in the high-ethanol exposure group.

Digitization accuracy

Four radiographs were redigitized. The coordinates for homologous points were compared statistically using least squares

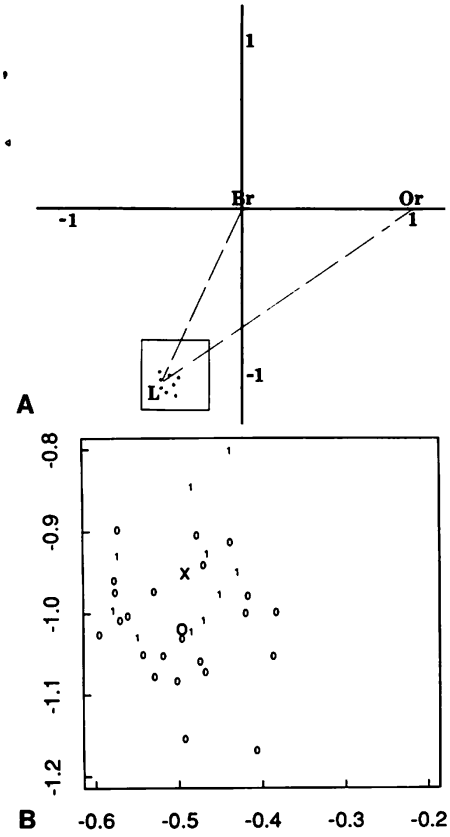

Fig. 3. **A:** Cartesian coordinates of scatterplot of shape coordinates for triangle Br-Or-L. **B:** Scatterplot of shape coordinates for triangle Br-Or-L. x,y coordinates for point L. O, control subjects; 1, high-dose ethanol subjects; 0, mean value of shape coordinates for control subjects; X, mean value of shape coordinates for high-dose ethanol subjects.

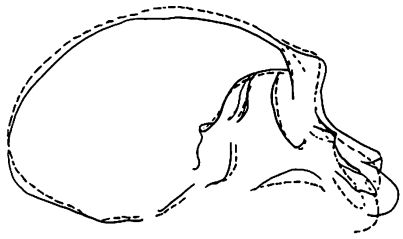

Fig. 4. Superimposition of radiographic tracings using "best fit" on anterior cranial base. Dysmorphic subject compared with age- and sex-matched control. Solid line, control (no. 1) female, 354 postconceptional days; dashed line, dysmorphic subject (no. 25) female, 352 postconceptional days.

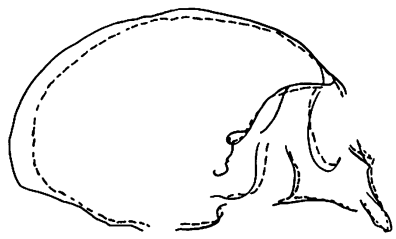

Fig. 5. Superimposition of radiographic tracings using "best fit" on anterior cranial base. Microcephalic subject compared with age- and sex-matched control. Solid line, control (no. 5) male, 332 postconceptional days; dashed line, microcephalic subject (no. 33) male, 326 postconceptional days.

TABLE 3. Statistical results of morphometric analysis of cranial shape

Age	No.	Landmarks	T-square	*P* value
1	33	Br-Or-L	6.11	.07
2	38	Br-Or-L	4.01	.16
1	33	Br-Or-S	3.88	.17
2	38	Br-Or-S	4.86	.11
1	33	Br-Or-L-S	6.39	.06[1]
2	38	Br-Or-L-S	5.23	.10[1]

[1]Computed from the average of the shape coordinates for triangles Br-Or-L and Br-Or-S.

analysis; digitization accuracy was determined to be high, with no shape coordinate varying by more than 2.6%.

DISCUSSION

It was hypothesized that a direct relationship would be found between increasing exposures to ethanol and the presence and degree of craniofacial malformations. The most severe craniofacial alterations were expected to occur in the group of animals that had been exposed to the higher weekly dose of ethanol from the beginning of gestation. The animal that was clinically dysmorphic was a member of the 1.8-g/kg cohort, the highest full-gestational dose exposure. The decreased protrusion of the midface, flattened philtrum, and long upper lip of

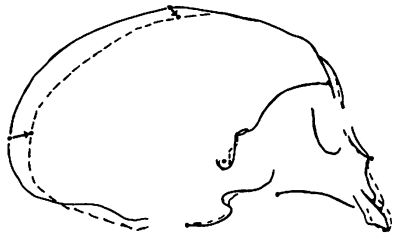

Fig. 6. Superimposition of radiographic tracings using "best fit" on anterior cranial base registered on points S and Or. High-dose ethanol subject compared with age- and sex-matched control. Solid line, control (no. 5) male, 206 postconceptional days. Coordinates of this subject were nearly identical to mean coordinates of the group combining the 16 low-ethanol exposure subjects with the 20 control animals. Dashed line, high-dose ethanol subject (no. 28) male, 206 postconceptional days. Coordinates of this subject were virtually coincident with mean coordinates of the group comprised of the 1.8-, 2.5-, 3.3-, and 4.1-g/kg cohorts. Arrows indicate the direction of distortion for points L and Br in the high-dose ethanol subjects, relative to the registration line S-Or.

TABLE 4. Longitudinal regression analysis of log of cranial area defined by Br-Or-S-L. (Seventy-two observations on a total of 45 subjects, 27 with area measured at two ages, 18 with area measured once)

	Coefficient[1]	Standard error
Age[2]		
Males	.00119	.00010
Females	.00101	.00012
Ethanol (1.8 g/kg)	.0353	.0207

[1]100 × (coefficient) reflects percentage changes in cranial area (because analysis is of log area).
[2]Postconceptional age in days.

animal 25 are all consistent with alcohol teratogenesis (Clarren and Smith, '78; Sulik et al., '81; Vtiz et al., '84). Other animals in the 1.8-g/kg cohort (nos. 24, 26, and 27) had been exposed to weekly plasma ethanol concentrations ranging from 189 mg% to 248 mg% but did not display perceptibly altered facial structures. Their calvaria were on average small and distorted when combined with the other high-exposure groups and compared with controls.

Apparently, early weekly gestational exposure to ethanol with peak plasma ethanol concentrations approximating 200 mg% can have an impact on facial form. Facial anomalies may relate to the specific dose schedule but could relate to other factors in teratogenesis, such as genetic susceptibility, maternal weight gain, or maternal alcohol dehydrogenase activity. Sulik suggested that a critical time period was likely to exist for the associated defects and malformations found in FAS (Sulik, '84). C57BL/6J mice exposed to ethanol doses ranging near 200 mg% on the seventh day of gestation had a 12% incidence of abnormalities of the nasal and upper lip regions that were characteristic of FAS (Sulik et al., '81; Sulik, '84). Newell-Morris and coauthors have demonstrated the craniofacial complex of *M. nemestrina* to be vulnerable to teratogenic influence by retinoic acid between days 20 and 44 of gestation (Newell-Morris et al., '80). Animal no. 25 was uniquely exposed to ethanol on days 24, 31, and 38, within this apparent period of embryonic vulnerability for facial anomalies. The DGE cohort animals received their initial ethanol doses (ranging from 260 mg% to 539 mg%) between days 33 and 46 postconception; no dysmorphic facial features were apparent in the DGE group. Further testing is needed to identify the critical period for the production of facial anomalies.

In this study, animals were sacrificed at age 6 months, which may explain the lack of significant findings in the analysis of facial features. A report detailing facial analysis of children exposed to varying gestational alcohol doses supported the contention that some children difficult to identify with FAS in infancy become more obviously affected later in childhood (Clarren et al., '87a). This will be investigated in a follow-up study in which animals exposed to gestational ethanol will be allowed to live to maturity.

The sole microcephalic animal in this study had been exposed to the highest dose of ethanol. This animal was part of the DGE cohort and had no ethanol exposure until the major period of organogenesis had ended. Microcephaly and scaphocephalic head shape have been reported in *M. nemestrina* exposed to an identical ethanol dose and schedule (Inouye et al., '85). Microcephaly, which is secondary to a diminished rate of brain growth, can be induced by weekly gestational exposure to extremely high doses of ethanol even if it is not administered until the major period of embryogenesis is completed.

In conclusion, a modest cohort ethanol effect was identified in this project, although the finding must be viewed as exploratory, since the analysis of animals

dosed at 1.8 g/kg or more was suggested by examination of the data rather than made as an a priori hypothesis. On average, animals exposed to high doses of prenatal ethanol had slightly smaller, distorted crania than control animals. Weekly exposure to gestational ethanol is therefore adequate to produce calvarial and facial alterations, but a dose-response threshold for dysmorphic effects and the time period critical for the effects have not been clarified. Further investigation using doses up to 1.8 g/kg administered early in gestation is planned to address these questions.

ACKNOWLEDGMENTS

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Maternal Marijuana Use During Lactation and Infant Development at One Year

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ASTLEY, S. J. AND R. E. LITTLE. *Maternal marijuana use during lactation and infant development at one year.* NEUROTOXICOL TERATOL **12**(2) 161–168, 1990.—Prenatal marijuana exposure is associated with adverse perinatal effects. Very little is known about the effect of postnatal marijuana exposure on infant development. Postnatal exposure can result from maternal use of marijuana during lactation. Delta-9-tetrahydrocannabinol (THC) transfers and concentrates in the mother's milk and is absorbed and metabolized by the nursing infant. The present study investigated the relationship between infant exposure to marijuana via the mother's milk and infant motor and mental development at one year of age. One hundred and thirty-six breast-fed infants were assessed at one year of age for motor and mental development. Sixty-eight infants were exposed to marijuana via the mother's milk. An additional 68 infants were matched to the marijuana-exposed infants on pre- and postpartum maternal alcohol and tobacco use. Marijuana exposure via the mother's milk during the first month postpartum appeared to be associated with a decrease in infant motor development at one year of age.

Lactation Marijuana Postnatal exposure Infant development

THE reported use of marijuana among pregnant women varies from five to 34 percent (4, 7, 8, 18). Fetal effects associated with prenatal exposure to marijuana include decreased birth weight (10,21) increased frequency of preterm delivery (2,7), increased labor and delivery complications (8,9) and altered visual, tremor and startle responses in neonates (3,6). Many of these findings remain suggestive due to the number of factors associated with marijuana use which are difficult to control in clinical and epidemiologic studies.

In contrast to the volume of literature addressing adverse effects of prenatal marijuana exposure, little attention has been directed towards postnatal marijuana exposure. Infant exposure via the mother's milk is of particular importance in light of the fact that delta-9-tetrahydrocannabinol (THC), the principal psychoactive component of marijuana, transfers into the mother's milk at levels reported at eight times that in maternal blood (17). Not only do nursing infants absorb and metabolize THC, but their exposure occurs at a time when growth and development, particularly glial and myalin formation in the central nervous system, is progressing at a rapid rate.

The purpose of this study was to investigate the relationship between infant marijuana exposure via the mother's milk and infant motor and mental development at one year of age in a predominantly middle class, low-risk population.

METHOD

Subject Selection

The research presented here uses data obtained in a previous prospective investigation of maternal diet, drinking and smoking during lactation on infant growth and development. There were three parts to the original prospective study. First, validity of self-reported alcohol, tobacco and other drug use and the reliability of the maternal interview process was confirmed (13,15). Next, descriptive studies were conducted to contrast the dietary habits and alcohol and tobacco use of lactating and nonlactating women (14, 19, 20). And finally, an infant assessment study was conducted that explored the relationship of alcohol use during lactation and infant development at one year of age (12).

Subjects in the previous prospective study were members of Group Health Cooperative of Puget Sound, a health maintenance organization in Seattle, WA. All prenatal patients receiving care between May 1, 1982 and July 1, 1984 were contacted by the Cooperative in their sixth month of pregnancy regarding possible study participation. An informed consent form with a full explanation of study procedures was provided. Seventy-four percent (5,298) of the prenatal patients responded and completed a mailed screening questionnaire detailing their alcohol and tobacco use both before and during pregnancy, some dietary information, and their plans to lactate. These patients constituted a screened pool.

Three months after delivery, 400 mother/infant pairs had been selected from the screened pool to participate in the previous infant assessment study cited above (12). Selection was based on maternal pre- and postpartum use of alcohol reported in personal interviews that were conducted at one and three months postpartum.

When the sample of 400 had been selected, we found that a substantial number of women reported postpartum use of mari-

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juana (n = 82). Seventeen additional women who reported marijuana use during pregnancy only were then taken from the screened pool to enrich the sample (n = 417) and provide sufficient power to conduct the pilot study described here. At one year of age, all 417 infants were assessed for motor and mental skills using the Bayley Scales of Infant Development (1).

From among the 417 infants with one-year assessments, those who had been breast-fed for at least two weeks with less than 16 ounces of supplemental formula per day were eligible for the present study. Three-hundred twenty-three of the 417 infants met this criteria. Of these 323 mother/infant pairs, 68 mothers (21%) reported marijuana use during the first and/or third month of lactation. The infants of these 68 mothers represent the "lactation-marijuana-exposed" group in this study. From the remaining 255 breast-fed infants whose mothers did not use marijuana during lactation (lactation-marijuana-unexposed), 68 were matched to the marijuana-exposed group on maternal alcohol and tobacco use during pregnancy and during the first and third months postpartum. The groups were also matched, as nearly as possible, on duration of lactation, prenatal marijuana exposure and month of birth. The two cohorts of infants (marijuana exposed and unexposed during lactation) make up the sample of 136 for the pilot study reported here.

Dependent Variables

The two outcome variables reflecting infant motor and mental development at one year of age were the Psychomotor Developmental Index (PDI) and Mental Developmental Index (MDI) from the Bayley Scales of Infant Development. The Bayley is a widely used infant assessment tool with a standard scoring system and demonstrated validity and reliability. The PDI index provided a measure of the infant's gross motor coordination and finer manipulatory skills of the hands and fingers. The MDI index provided a measure of the infant's problem solving abilities and verbal communication development. The examiners were trained master's level clinicians with specialities in infant development. They were blind to the drug use status of the mother. Interobserver reliability on Bayley scores was maintained at 0.9 or higher.

Independent Variables

Personal interviews were conducted at one and three months postpartum in the original prospective study to gather detailed information on alcohol and tobacco use, exposure to other drugs (prescriptions, over-the-counter drugs, marijuana and other illegal substances), demographic characteristics, obstetric history, lactation status and use of supplemental formula during lactation. The use of drugs during pregnancy was addressed retrospectively in the one-month postpartum interview. Each subject had been assigned a single interviewer for the duration of the study. The interviewers were women of childbearing age, trained to obtain valid and reliable information. Validity of self-reported drug use was confirmed in an earlier pilot investigation on a sample of 108 randomly selected postpartum women. Self-reported drug use was compared to laboratory tests of drug levels present in body fluids; the proportion of questionable self-reports ranged from 0 to 3% depending on the drug (13).

Maternal use of marijuana, cocaine, caffeine and other drugs was measured in terms of how often the substance was used, when it was used and how much was used. Alcohol consumption was categorized into beer, wine and liquor and was measured in terms of frequency of use, modal quantity, and maximum quantity per drinking occasion. These measures were converted to average daily ounces of ethanol ingested in a specified period of time

TABLE 1

CHARACTERISTICS OF WOMEN WHO DID AND DID NOT USE MARIJUANA DURING LACTATION

Maternal Characteristics	Marijuana Use During Lactation (N = 68)	No Marijuana Use During Lactation (N = 68)
	N or Mean ± Standard Deviation	
Age (years)		
18 to 29	42	41
30 to 41	26	27
Race		
White	63	68
Parity		
Primiparous	42	39
Marital status		
Married	57	60
Income		
<$10,000	10	4
$10,000 to $25,000	28	32
>$25,000	30	32
Postpartum working status		
Employed	8	8
Education (years)		
10 to 12	24	23
13 to 15	20	25
16 to 23	24	20
Maternal height (cm)	167 ± 6	166 ± 6
Pregnancy weight gain (kg)	16 ± 4	15 ± 5
Lactation duration		
≤One month	10	10
Two months	9	7
Three months	45	49
One or more months*	4	2
Supplemental formula use during lactation (<16 oz./day)		
Month one	9	10
Month three	15	13
Infant sex		
Female	30	33
Gestation (weeks)	40 ± 2	40 ± 1

*Lactation status unknown for 2nd and 3rd months postpartum.

("AA score") (11). For cigarette use, a nicotine score was determined by multiplying the number of cigarettes smoked per day by the nicotine content of the brand specified. Use of supplemental formula was recorded as no use, <16 ounces per day or >16 ounces per day.

The primary independent variable in this study was the number of days an infant was exposed to marijuana via the mother's milk during postpartum months one and three. The frequency of maternal marijuana use weighted by the mother's duration of lactation provided an estimate of infant exposure to marijuana via breast milk.

Secondary independent variables which could potentially con-

TABLE 2
MATERNAL MARIJUANA USE DURING PREGNANCY AND LACTATION

Maternal Marijuana Use	Pregnancy N = 136		Lactation Month One N = 136		Lactation Month Three N = 125*	
	N	(%)	N	(%)	N	(%)
Frequency						
Never	70	(52)	81	(60)	72	(58)
<once a week	38	(28)	27	(20)	22	(18)
1–4 times a week	20	(15)	18	(13)	18	(14)
Daily	8	(5)	10	(7)	13	(10)
Number of times per day						
0	70	(52)	81	(60)	72	(58)
1	55	(40)	47	(35)	38	(30)
2	7	(5)	5	(3)	9	(7)
3 to 5	4	(3)	3	(2)	4	(3)
Unknown	0	(0)	0	(0)	2	(2)

*Eleven subjects selected too late for third month interview.

found the relationship between infant marijuana exposure during lactation and infant development included: 1) Maternal age, height, race, income level, education, marital status, pregnancy history and weight gain, tobacco, coffee, alcohol and psychoactive drug use during pregnancy and lactation and marijuana use during pregnancy; 2) Paternal alcohol and tobacco use before conception and during the postpartum period; 3) Infant gestational age and sex.

Maternal dietary history was gathered in the original study, but previous studies of this population have revealed no association between infant development and maternal nutrition (12,19).

Statistical Analysis

Standard multiple regression analysis was used to determine if infant exposure to marijuana via breast milk explained a significant proportion of the variance in the infant motor and mental development scores, after controlling for confounding and interaction with other independent variables.

The first stage of analysis began with the transformation of the categorical measures of maternal marijuana use into continuous measures that reflected infant exposure. In utero exposure was represented by the number of days the mother used marijuana in each trimester. Infant exposure via the mother's milk was represented by the number of days the mother used marijuana during postpartum months one and three, weighted by the proportion of days she lactated in each month. For example, an infant whose mother reported daily use of marijuana during postpartum month one and stopped breast-feeding halfway through the month would receive an estimated exposure score of fifteen days. An infant whose mother reported marijuana use every other day and breast-fed throughout the month would also receive an exposure score of fifteen days. Women who reported use of less than 16 ounces of supplemental formula during lactation were classified together with women that reported no use of supplemental formula. The effect of supplemental formula use on infant marijuana exposure in this study is addressed in the analysis.

TABLE 3
INFANT MARIJUANA EXPOSURE

Exposed During Gestation	Exposed During Lactation	Number of Subjects
NO	NO	58
YES	NO	10
NO	YES	14
YES	YES	54

Next, potential confounding variables were identified by assessing their association with both infant developmental outcome (MDI or PDI) and maternal use of marijuana during lactation. Chi-square, regression analysis and ANOVA were used, where appropriate, to evaluate associations of each variable with exposure and outcome. We did not, however, rely on statistical significance to identify potential confounders. Any variable that demonstrated a suggestive association with both exposure and outcome was retained as a potential confounder. All secondary variables identified as confounders were regressed simultaneously with infant marijuana exposure during lactation on infant PDI and MDI outcome measures. Backwards and stepwise variable selection was performed with F-to-enter set at $p = 0.05$ and F-to-remove set at $p = 0.10$. Pairwise deletion of missing data was employed. Interaction terms between infant marijuana exposure during lactation and each retained secondary variable were computed. Each interaction term was allowed to enter the equation containing the interaction component variables by stepwise selection to determine if any secondary variable significantly modified the effect of marijuana exposure on infant PDI and MDI. Finally, maternal use of cocaine, alcohol and tobacco during pregnancy and lactation were forced into the final equation, one at a time, to verify that addition of the variable did not change the estimate of the primary independent variable.

Differences in maternal characteristics between the women who did and did not use marijuana during lactation were determined by chi-square or the *t*-test. Contrasts and linear trends of mean MDI and PDI scores, stratified by infant marijuana exposure during gestation and lactation were evaluated with one-way ANOVA.

RESULTS

There were no significant differences between the sociodemographic profiles and infant characteristics of the women who did and did not use marijuana during lactation, as shown in Table 1. Both groups were primarily white, middle class, college-educated women. Age ranged from 18 to 41 with a mean of 28.3 years. Eighty-six percent of the women were married.

The frequency of maternal marijuana use during pregnancy and lactation is presented in Table 2. Twenty to 24 percent of the women in this study reported using marijuana at least once a week during pregnancy or lactation. The usual dose on each occasion was one joint. Five to ten percent of the women who used marijuana reported smoking two to five joints per day. Of the women who reported using marijuana during pregnancy, 84% continued to use marijuana during lactation (Table 3). This strong correlation between maternal pre- and postpartum marijuana use could not be effectively reduced by matching (Pearson correlation coefficient = .59). Matching did, however, effectively reduce the correlations between marijuana use during lactation and the pre- and postpartum use of alcohol and tobacco (Table 4). Alcohol, tobacco and cocaine use during pregnancy and lactation was comparable between the women who did and did not use mari-

TABLE 4

MATERNAL ALCOHOL, TOBACCO AND COCAINE USE

	Marijuana Use During Lactation (N=68)			No Marijuana Use During Lactation (N=68)		
Drug Use	Mean	(S.D.)	N	Mean	(S.D.)	N
Alcohol use: AA score*						
One month prior to conception	0.96	(0.84)	68	0.75	(0.73)	68
During pregnancy	0.14	(0.21)	68	0.20	(0.33)	68
During lactation month one	0.41	(0.39)	68	0.45	(0.54)	68
During lactation month three†	0.57	(0.67)	59	0.53	(0.47)	64
Tobacco use: Average daily mg nicotine						
During pregnancy	3.6	(6.9)	66	3.8	(6.8)	65
During lactation month one	4.7	(8.2)	66	4.5	(7.9)	67
During lactation month three†	6.2	(9.2)	57	5.3	(8.0)	64
Cocaine use: Frequency						
During pregnancy						
never			59			65
<once a month			8			3
2–3 times a month			1			0
During lactation month one						
never			65			68
<once a month			2			0
once a month			1			0
During lactation month three†						
never			60			62
once a month			1			2
unknown			7			4

*The AA score reflects the absolute ounces of ethanol ingested daily.
†Eleven subjects selected too late for the third month interview.

juana during lactation. The Pearson correlation coefficients between these variables were all less than .08. There was also no significant correlation between marijuana use during lactation and consumption of coffee.

For descriptive purposes, the mean MDI and PDI scores, stratified by infant marijuana exposure, are presented in Table 5. Higher exposure was defined as exposure to marijuana for more than half of the days of the period. Infants exposed to marijuana for more than half of the days during the first trimester or the first month of lactation had significantly lower mean PDI scores than infants with no marijuana exposure during these periods (one-way ANOVA, $p=0.02$, and 0.008, respectively). Moderate marijuana exposure (exposure for no more than half of the days in a period) only appeared to affect infant PDI in the first trimester. Mean infant PDI scores decreased linearly with increasing marijuana exposure during this period (linear trend, $p=0.005$). Very little change was reflected in the mean mental score.

When the secondary independent variables listed above were examined to determine if they might be the cause of the difference in PDI seen in Table 5, only the measure of maternal marijuana use during pregnancy was a potential confounder. Maternal race (white versus nonwhite) demonstrated a near significant association with both lactation exposure and infant motor development and was retained for further study.

Variables initially regressed on infant motor development (PDI) were maternal race and the number of days that infants were exposed to marijuana during each trimester and the first and third months of lactation. Of these variables, infant exposure to marijuana via the mother's milk during the first month postpartum was the only variable identified by stepwise and backward selection that explained a significant proportion of the variance in infant motor development (Table 6). Five percent of the variance was explained by the infant's exposure to marijuana during this period. Infant exposure expressed as the number of joints smoked by the mother during lactation did not change the results.

The only variables regressed on infant mental development were the number of days that infants were exposed to marijuana during lactation months one and three because no secondary variables were identified as confounders. No significant associations were found.

Exposure to cocaine via breast milk and alcohol during gestation also had a significant adverse effect on infant PDI (Table

TABLE 5

MEAN MOTOR AND MENTAL DEVELOPMENT SCORES* CORRESPONDING WITH MARIJUANA EXPOSURE DURING GESTATION AND LACTATION

		Motor Development PDI			Mental Development MDI		
Days of Infant Marijuana Exposure		Mean	(S.D.)	Range	Mean	(S.D.)	Range
Trimester one†							
0	(n=84)	105	(17)	70–150	107	(15)	72–150
1 to 44	(n=36)	99	(17)	66–147	108	(15)	77–134
45 to 90	(n=16)	93	(16)	75–136	106	(13)	89–128
Trimester two							
0	(n=98)	102	(17)	66–150	106	(15)	72–150
1 to 44	(n=25)	104	(19)	66–147	111	(12)	86–128
45 to 90	(n=13)	94	(16)	76–136	106	(14)	84–128
Trimester three							
0	(n=94)	101	(17)	66–150	107	(15)	72–150
1 to 44	(n=28)	107	(17)	86–147	109	(14)	86–128
45 to 90	(n=14)	94	(16)	76–136	106	(14)	84–128
Lactation month one‡							
0	(n=81)	102	(18)	66–150	109	(15)	77–150
1 to 14	(n=38)	106	(16)	82–145	105	(12)	84–128
15 to 30	(n=17)	90	(14)	66–117	106	(15)	72–128
Lactation month three§							
0	(n=84)	102	(18)	66–150	107	(15)	77–150
1 to 14	(n=28)	103	(16)	71–134	110	(13)	89–134
15 to 30	(n=13)	97	(16)	76–136	108	(17)	72–128

*Motor and mental developmental scores (PDI, MDI) were from the Bayley Scales of Infant Development.

†PDI decreased with increasing marijuana exposure, test for linear trend, $p=0.005$.

‡Mean PDI for the higher exposure group was lower than the PDI for the no or low exposure groups, one-way ANOVA $p=0.008$.

§Eleven subjects selected too late for third month interview.

7). Inclusion of cocaine and alcohol exposure variables in the above model explained an additional nine percent of the variance in infant PDI scores. Alcohol and cocaine exposure did not confound or interact with the effect of marijuana exposure during lactation on infant PDI, nor did the removal of the five subjects with reported cocaine use during lactation.

Thirty-eight of the 136 women reported use of supplemental formula (less than 16 ounces per day) during the first and/or the third month of lactation. Twenty-two of these women were in the marijuana-exposed group. In this study, women who used less than 16 ounces of supplemental formula during lactation were classified with the women who reported no use of supplemental formula. This classification scheme could result in a slight overestimate of infant marijuana exposure via breast milk, and thus underestimate the strength of the relationship between marijuana exposure and infant development. Restricting the analysis to those women who reported no use of supplemental formula at any time (n=98) did, in fact, strengthen the association between marijuana exposure during the first month of lactation and infant motor development. Eight percent of the variance in infant motor development was explained by the infant's exposure to marijuana during this period, $F(2,87)=7.3$, $p=0.001$. Exposure to cocaine throughout lactation explained an additional six percent of the variance. Alcohol exposure during gestation no longer explained a significant amount of the variance in infant motor development in this subset of infants.

DISCUSSION

In this study sample, daily infant exposure to marijuana via the mother's milk during postpartum month one was associated with a 14 ± 5 point decrease in the Bayley index of infant motor development. This adverse effect on infant PDI was noted in spite of the low-risk status of the study population. The finding persists after controlling for maternal smoking, drinking and cocaine use during pregnancy and lactation.

Marijuana exposure during the first trimester, however, confounded the association between marijuana exposure during the first month of lactation and infant PDI. Stepwise and backwards variable selection procedures identified marijuana exposure during the first month of lactation as the stronger predictor of infant PDI, but the strong correlation between marijuana exposure during the first trimester of pregnancy and the first month of lactation makes it difficult to reliably determine which period of exposure had a stronger influence on infant motor development.

One way to assess the relative importance of independent variables is to consider the increase in r^2 when a variable is entered into an equation that already contains the other independent

TABLE 6

MATERNAL RACE AND INFANT MARIJUANA EXPOSURE DURING GESTATION AND LACTATION REGRESSED ON INFANT PDI

Variable in the Equation	B	S.E. of B	Beta	T	Sig. T
Days of marijuana use during lactation month one	−0.46	0.18	−0.22	−2.50	0.013
Constant	103.42	1.62		64.0	0.000
$F(1,123) = 6.24$ $p = 0.013$ $r^2 = .049$					
Variables Not in the Equation	**Beta in**	**Partial**	**T**	**Sig. T**	
Days of Marijuana use:					
trimester one	−0.044	−0.035	−0.39	0.69	
trimester two	0.021	0.017	0.19	0.85	
trimester three	0.040	0.032	0.36	0.72	
lactation month three	−0.016	−0.014	−0.16	0.87	
Maternal race	−0.059	−0.06	−0.68	0.50	

Dependent variable: PDI (infant Psychomotor Developmental Index from the Bayley Scales of Motor Development).

variables (16). A large change in r^2 indicates that a variable provides unique information about the dependent variable that is not available from the other independent variables in the equation. The addition of first trimester marijuana exposure to a model containing marijuana exposure during the first month of lactation resulted in a change in r^2 of only .001 (Table 8). On the other hand, the addition of the first month lactation exposure to a model containing first trimester marijuana exposure resulted in a change in r^2 of .023 suggesting that marijuana exposure during the first month of lactation contributes unique information about the variance in infant PDI, above and beyond the information provided by first trimester exposure. Further evidence suggesting a weak or perhaps nonexistent association between first trimester exposure and infant PDI can be seen in the low F value when first trimester exposure is regressed separately on infant PDI.

TABLE 7

VARIABLES IDENTIFIED BY STEPWISE MULTIPLE REGRESSION, THAT EXPLAINED A SIGNIFICANT PROPORTION OF THE VARIANCE IN INFANT PDI

Independent Variables	B	S.E. of B	T	Sig. T	r^2
Days of marijuana use during lactation month one	−0.46	0.18	−2.58	0.011	.05
Pregnancy AA score*	−13.85	5.21	−2.66	0.009	.05
Days of cocaine use throughout lactation	−10.73	4.77	−2.25	0.026	.04
Constant	106.23	1.81	58.4	0.000	
$F(3,121) = 6.54$ $p = 0.0004$ $r^2 = .14$					

*The AA score reflects the absolute ounces of ethanol ingested daily.

Dependent variable: PDI (infant Psychomotor Developmental Index from the Bayley Scales of Motor Development).

A linear model provided the best fit of the data, despite the threshold appearance of the relationship between marijuana exposure during the first month of lactation and infant motor development (Table 5). A linear fit is certainly not inconsistent with the results presented in Table 5. When continuous data is presented in a categorized format, an apparent threshold or linear effect can be created simply by virtue of where you decide to divide the categories. Further study, preferably with larger samples will be

TABLE 8

MARIJUANA EXPOSURE DURING THE FIRST TRIMESTER OF PREGNANCY AND THE FIRST MONTH OF LACTATION REGRESSED ON INFANT PDI*

Days of first trimester marijuana exposure regressed on infant PDI

PDI = 102.9 − 0.12 (mj-1st trimester)

S.E. = 0.07 $p = 0.07$ $F(1,134) = 3.67$ $p = 0.07$ $r^2 = .026$

Days of marijuana exposure during lactation month one regressed on infant PDI

PDI = 103.4 − 0.46 (mj-lactation)

S.E. = 0.18 $p = 0.01$ $F(1,134) = 6.80$ $p = 0.01$ $r^2 = .049$

Days of marijuana exposure during trimester one and lactation month one regressed simultaneously on infant PDI

PDI = 103.5 − 0.03 (mj-1st trimester) − 0.41 (mj-lactation)

S.E. = 0.08 $p = 0.68$ S.E. = 0.22 $p = 0.07$ $F(2,133) = 3.46$ $p = 0.03$ $r^2 = .050$

*PDI: Psychomotor Development Index from the Bayley Scales.

necessary to determine the true nature of the association between PDI and marijuana exposure via breast milk.

To date, only one published report has assessed the relationship between infant exposure to marijuana via breast milk and infant development at one year of age (18). In this study, Tennes and her colleagues compared a subset of 27 infants exposed to marijuana via breast milk to 35 breast-fed infants who were not exposed to marijuana. Of the women that reported marijuana use during lactation, twelve used it once a month or less, nine reported weekly use and six used it daily. Prenatal marijuana exposure was not reported for this group. At one year of age the infants were assessed for motor and mental skills using the Bayley Scales of Infant Development. Unlike the present study, no apparent effects of postnatal marijuana exposure were found. The investigators did note, however, that the statistical analyses were limited due to the small sample size and lack of comparability among cases for duration of exposure and dose.

In a study of prenatal effects of marijuana exposure on infant development (2), Fried reported that babies born to women who smoked more than five joints per week during pregnancy demonstrated marked tremors and startles and altered visual responsiveness at two to four days of age. These symptoms attenuated within 30 days. A follow-up study found no association between prenatal marijuana exposure and infant motor development (PDI) at one and two years of age (5). In the present study, prenatal marijuana exposure also failed to be associated with infant motor development when measured at one year of age. Postnatal marijuana exposure, however, did appear to be significantly associated with one-year motor development scores in the present study. Measures of postnatal marijuana exposure were not available in the two studies reported by Fried.

Despite the slight increase in maternal use of marijuana during the third month of lactation in the present study, there was no significant effect on infant PDI associated with marijuana use at that time. It is unlikely that this is due to the decrease in the sample size by eleven subjects in the third month postpartum. The study had the power to detect a difference of eight points in the motor development index with ninety percent certainty in the third month. An increase in the use of supplemental formula also failed to explain the lack of association between infant motor development and marijuana exposure during the third month of lactation. Use of supplemental formula would reduce infant marijuana exposure via breast milk, but exclusion of women who used supplemental formula failed to strengthen the association. This lack of effect on infant PDI may reflect a decrease in developmental vulnerability in postpartum month three.

Maternal use of marijuana during pregnancy and lactation had no detectable effect on infant mental development at one year of age in this study. A lack of association between prenatal exposure and mental development at one and two years of age has also been reported by Fried (2,5). The lack of association seen in all three studies suggests that the neurological areas associated with cognitive function may be less vulnerable to marijuana exposure. Further studies using larger sample sizes, higher exposure and more sensitive diagnostic tools are needed to support this finding.

Daily exposure to marijuana during the first month of lactation was associated with a decrease in PDI score of 14 points, which represents three quarters of a standard deviation in the infants of this sample. It is a difference large enough to be detected by an astute clinician. The long-term implications for child development, however, are unknown. Evaluation of infant mental and motor development is not straightforward, and interpretation of the findings is not always easy.

In summary, although marijuana exposure during lactation was associated with decreased infant motor development, this result should be interpreted cautiously due to the preliminary nature of this study. One cannot infer from the results presented here that marijuana exposure during lactation impairs infant motor development at one year of age, or that prenatal marijuana exposure does not impair motor development. Marijuana exposure during lactation appeared to be a better predictor of infant motor development, but it does not necessarily mean that the relationship is one of cause and effect. Prenatal marijuana exposure, passive exposure to marijuana smoke in the air and the quality of maternal/infant interactions are three factors that could potentially confound the observed association in this study. The difficulty of evaluating infant development and the predictive value of the findings should also be considered. Nevertheless, the deleterious effects of maternal drug use on infant development may not be limited to prenatal exposure; postnatal exposure may be playing a critical role and warrants consideration in future investigations.

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Neuroanatomic and Neurochemical Abnormalities in Non-human Primate Infants Exposed to Weekly Doses of Ethanol during Gestation

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Ethanol was orally administered once per week to 54 gravid pigtailed macaques (*Macaca nemestrina*) in doses of 0.0, 0.3, 0.6, 1.2, 1.8, 2.5 or 4.1 gm/kg from the 1st week in gestation or in doses of 2.5, 3.3 or 4.1 gm/kg from the 5th week. Mean maternal peak plasma ethanol concentrations (MPPEC's) ranged from 24 ± 6 mg/dl at the 0.3 g/kg dose to 549 ± 71 mg/dl at the 4.1 g/kg dose. Thirty-three live born infants were assessed for abnormalities of physical and behavioral development. Ocular pathology, neuropathologic and neurochemical assessments were done on 31 animals at 6 months postnatal age. Microphthalmia was noted in three of the 26 animals exposed to ethanol. Retinal ganglion cell loss was significantly associated with intra-uterine ethanol exposure. Microphthalmia and retinal ganglion cell loss was observed in both the delayed and full-gestational exposed animals. No structural anomalies were found in the brains via gross inspection or light microscopy. Chemical abnormalities in the striatal nuclei were identified. Striatal dopamine concentrations increased with increasing MPPEC exposure (0–249 mg/dl) among animals exposed weekly to ethanol throughout gestation. Striatal dopamine concentrations decreased with increasing MPPEC exposure (260–540 mg/dl) among animals whose weekly exposure to ethanol was delayed until the 5th week of gestation. The same pattern of association was also noted between MPPEC and ultrastructural alterations in the caudate nucleus. The extent of ultrastructural alterations increased with increasing MPPEC among the full-gestational exposed animals and decreased with increasing MPPEC among the delayed-dose animals.

CENTRAL NERVOUS SYSTEM (CNS) dysfunction is well established as one of the most important clinical results of ethanol teratogenesis. CNS dysfunction is part of the definition of fetal alcohol syndrome (FAS).[1,2] Yet, little is known about where in the brain, when in gestation, or by what mechanisms ethanol-related CNS teratogenic changes occur. This report summarizes an extensive survey of brain chemistry and anatomy performed on 31, 6-month old nonhuman primates (*Macaca nemestrina*). The data are part of the results of a much larger project designed to assess the teratogenic impact of once-per-week alcohol use during pregnancy. Once-per-week alcohol consumption has been found to be the most frequent intermittent consumption pattern for alcohol use by American women.[3]

In the overall project, ethanol was administered orally once a week throughout gestation (from week 1–24) to gravid pigtailed macaques (*M. nemestrina*) in doses of 0.3, 0.6, 1.2, 1.8, 2.5, 3.3, or 4.1 g/kg. A control group received a weekly, oral sucrose solution that was isocaloric and isovolumetric to the highest ethanol dose. The pregnancies were managed normally in all ways aside from the weekly dosing. Weight gain and health were monitored in all gravid animals. The ethanol exposures had a negligible impact on the general health and activity of the mothers, although the animals exposed to the higher ethanol doses (above 1.8 g/kg) were mildly subdued for several hours after each dosing. Previous reports of results from this project have described the general study design, the pregnancy outcomes, and the physical problems and developmental delays of the infants.[4–6]

To briefly summarize those previous reports, pregnancy was followed in 54 females after 116 matings resulting in 33 live born infants. Two infants developed serious infectious illnesses and died within the 1st month of life. Mean maternal peak plasma ethanol concentrations (MPPECs) ranged from an average of 24 ± 6 mg/dl at the 0.3 g/kg dose to 549 ± 71 mg/dl at the 4.1 g/kg dose. The goal of the study was to produce seven viable infants in each dose cohort for assessment of mental and motor development. The proportion of pregnancies that failed within the first 30 days of gestation in the 0.3, 0.6, 1.2, and 1.8 g/kg ethanol cohorts were 67% (14/21), 56% (9/16), 60% (9/15), and 36% (5/14), respectively. The pregnancy failure rates in these cohorts were not statistically different from the rate of 50% in the 14 timed-matings in the study control group, nor were they different from the overall rate of 50% in the primate colony based on more than 1000 timed-matings. At the 2.5 g/kg dose, however, five of six females (83%) experienced pregnancy failure in the first 30 days of gestation. The one animal that was con-

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firmed to be pregnant, aborted by the end of the first trimester. Although this increased rate was not significantly different from the control rate, this rate was too high to produce seven viable infants in the time allocated for the study. At the 4.1 g/kg dose, seven of seven (100%) of the pregnancies failed, and this was significantly higher than the rate for the study control group ($p = 0.008$, binomial test). Since the purpose of the study was to produce viable infants for developmental assessment, there was nothing to be gained by continuing the administration of these two fetotoxic doses. In order to study a small sample of infants exposed to very high doses of ethanol and to provide preliminary data for an alternate exposure pattern, the decision was made to delay the administration of high dose ethanol until the 5th week of gestation. The pregnancy failure rates for the delayed exposure group as a whole dropped from 92% (12 of 13) to 52% (12 of 23), as anticipated.

The number of infants in each exposure cohort that was available for neuroanatomic and neurochemical assessment at 6 months of age is presented in Fig. 1 in which full blackened circles denote that the individual deviated by more than two standard deviations from control group means. At least one of the hallmark features of human FAS: facial anomalies, growth deficiencies or central nervous system dysfunction, were found in 57% of the ethanol-exposed animals. No individual animal showed the complete human FAS pattern. Six of the nine animals (67%) exposed to MPPECs at or above 115 mg/dl starting in the 1st week of gestation had clear evidence of a teratogenic impact. While three of the six infants (50%) exposed to higher, delayed doses showed some evidence of a teratogenic effect, none of 11 animals exposed to lower, full-gestational exposures showed comparable effects.

The six animals with full-gestational exposure and MPPECs between 140 and 249 mg/dl had much more severe and consistent cognitive abnormalities than the animals with the delayed gestational exposures, even though the latter were exposed to MPPECs between 260 and 540 mg/dl (Fig. 1).

The study results are consistent with clinical impressions that ethanol related behavioral teratogenesis may occur without accompanying physical anomalies. In addition, the preponderance of abnormalities from ethanol-induced teratogenesis from a once-per-week exposure frequency occurred with MPPECs above 140 mg/dl—an intoxicating dose in humans which can be achieved through the consumption of four to six standard drinks by an average sized woman. Finally, and intriguingly, early gestational exposure to ethanol appeared to be more damaging to cognitive function than later with considerably greater ethanol exposure.

METHODS

After extensive study of their physical and behavioral development, the animals were killed at approximately 6 months of age (329 to 380 days postconception). An initial intramuscular injection of ketamine (10 to 15 mg/kg) was given. If adequate sedation was not achieved, a second (and occasionally a third) dose of ketamine was employed. Once the animal was deeply sedated, an intravenous line was placed in an exposed saphenous vein through which chloral hydrate (40 mg/kg) was infused. Blood pressure was monitored continuously. An adequate surgical level of anesthesia was achieved when the animal exhibited no foot withdrawal reflex and no significant change in blood pressure to deep pressure stimulation. When this level of anesthesia was reached, the optic globes were enucleated with the optic nerves and the brain was removed. The eyes were immediately transferred for study (Dr. Milam's laboratory). The brain was weighed and inspected for gross morphological abnormalities. The cerebellum and brain stem were separated from the cerebrum at the level of the midbrain and the cerebral hemispheres were bisected along the midsagittal plane. The left hemisphere was then placed, mesial surface down, on a frame with a clear Plexiglas bottom. For cutting in coronal plane, the hemisphere was positioned by aligning the anterior and posterior commissures and the massa intermedia. A specially designed, multiblade knife was drawn across the hemisphere producing a series of 5-mm thick cerebral slices. The slices were spread on a dissection board for anatomic identification. Simultaneously, free hand dissection was done of the right hemisphere by a second dissector. That hemisphere was sectioned coronally at the level of the anterior commissure and 5 mm rostrally. Tissues for neurochemical analysis of dopamine, DOPAC, norepinephrine, epinephrine, and serotonin were obtained through dissection from the 5-mm thick slices from the left hemisphere. Structures sampled included the substantia nigra, hypothalamus (with mammillary body), frontal gyrus, calcarine cortex, hippocampus, and hemibrain stem, as well as the right preoptic area and putamen and caudate nuclei. These samples were frozen immediately on dry ice for later analyses (Dr. Shoemaker's laboratory).

The left caudate and putamen were dissected in toto from each brain slice, placed on ice and transferred for immediate assay for dopamine receptors using the ligand-binding technique (Dr. Lai's laboratory).

Samples from the left preoptic area, gyrus rectus, calcarine cortex, right caudate and putamen nuclei, and right cerebellar cortex were placed in Karnovsky's solution for electron microscopic assessment (Dr. Rudeen's laboratory).

Except for portions of the hippocampal gyrus, cerebellum, hypothalamus, and brain stem, which will be utilized in other studies not yet completed, all remaining brain tissues were placed in 10% neutral buffered formalin for neuropathologic study (Dr. Clarren's laboratory). The entire dissection was completed in less than 8 min from the moment the calvarium was removed and the superior sagittal sinus was ruptured.

Tissue sent to each investigator was coded so that the analyses were done without knowledge of the animals' exposure history.

Neuropathology

The right hemisphere was received as two formalin fixed pieces with a 5-mm coronal section missing at the approximate level of the lateral geniculate. The pieces were photographed and sectioned coronally in standard 5-mm slices. After gross inspection and photography, the slabs were embedded in paraffin, cut, mounted, and stained with hematoxylin and eosin as well as luxol fast blue-nissl. The slides were studied in two ways. First, all samples from the same animal were scanned. Then, similar sections from all the animals were compared. Particular attention was paid to detecting cortical irregularities especially in the hippocampus and calcarine areas, white matter loss or gliosis, and neuronal density and structure. Heterotopias were specifically sought.

Ocular Pathology

The globes were slit at the pars plana and placed immediately in 2% paraformaldehyde and 2% glutaraldehyde in 0.13 M phosphate buffer. The gross pathology assessment included measurement of the cornea (horizontal and vertical diameters) and of the globe (horizontal, vertical,

and anterior-posterior diameters). Each globe was opened horizontally and the anterior segment and fundus were examined for abnormalities. A horizontal segment of retina 10 mm wide and 5 mm high was dissected, which included the optic nerve head and the fovea. The tissue was dehydrated, embedded in Sorvall JB-4 methacrylate, and sectioned at 4-μm thickness. Sections were selected that included the fovea pit and optic nerve head and were stained with Richardson's methylene blue-azure II mixture. Ganglion cell counts were recorded from a 1-mm zone of retina extending from the nasal and temporal sides of the fovea pit. The counts were performed at magnification ×40 by three independent investigators. Ganglion cell counts were expressed as normal (7–8 cells deep), mild loss (5–6 cells deep), and marked loss (4 cells deep).

Electron-Microscopic Assessment

Each tissue sampled was fixed in Karnovsky's fixative and trimmed to rectangular blocks approximately 1 × 2 × 1 mm. The tissue blocks were embedded in an Epon 812 resin by standard techniques.[7] The tissues were thin-sectioned with an ultramicrotome and the sections retrieved from the water trough on the glass knife with single-slot copper grids. The grids were placed on formvar films, allowed to air dry then stained with uranyl acetate and lead citrate to enhance the contrast of the tissue. The tissue sections were observed using a Zeiss 10-CR electron microscope. Individual cells from different blocks were selected, photographed and the images printed (final magnification: ×2,550–4,000). To maximize the possibility of finding a structural difference due to ethanol exposure, tissues from the six delayed-dose exposed animals and six full-gestational exposed animals with MPPECs ≥124 mg/dl were compared with tissues from the five control animals. The evaluation involved the subjective estimate of the degree of abnormal appearance of the following cellular parameters: rough endoplasmic reticulum, Golgi bodies, mitochondria, nuclear morphology and heterochromatin pattern, and general cytoplasmic appearance. A scoring system for assessing these ultrastructural alterations of the cell and its organelles was used in which a value of 1 represented the normal appearance without any apparent morphological aberration; 2, a nominal alteration of the normal appearance; 3, a moderately altered appearance; 4, a substantial degeneration in the normal appearance of the cell or its organelles; and 5, a maximal abnormal appearance of cellular structure.

Neurochemical Analysis

The sample vials were removed from the freezer and thawed in a cold water bath. Three milliliters of cold 0.1 M $HClO_4$ was added to each sample, and the tissue was homogenized using a Tekmar TR-10 Tissuemizer adapted with a microprobe. The homogenate was spun for 20 min in a refrigerated Sorvall RC-3 centrifuge at 1,300 rpm. The supernatant was removed and transferred to a 3.5-ml conical bottom assay tube. The remaining pellet was reserved for total protein analysis. One milliliter of 1.5 Tris buffer contaminating EDTA with an adjusted pH of 8.6 was added to each tube along with 50 mg of AAO (acid-washed aluminum oxide). Next, 100 mg/ml of 3,4-dihydroxybenzylanine (DHBA) was added as an internal standard. The tubes were capped, gently shaken for 20 min, centrifuged, and the supernatant aspirated. The remaining AAO was washed with 1 ml of 0.005 Tris buffer, centrifuged and the supernatant again aspirated. This washing was repeated two more times to thoroughly clean the AAO. To extract the catecholamines from the AAO, 200 μl of 0.4 M $HClO_4$ was added to each tube. The tubes were gently shaken for 10 min and then centrifuged. The supernatant was removed, and the samples were transferred to vials and refrigerated until separations were performed.

Epinephrine, norepinephrine, serotonin, dopamine, and DOPAC were separated on an Isocratic liquid chromatography system consisting of a Waters M6000A dual piston pump and a Waters model 712 sample processor equipped with refrigeration unit set at 10°C. An ESA model 5100A coulochem electrochemical detector equipped with an ESA HR 80 column was used for amine detection. A two cell system was employed. The first cell was a +0.04V charge to neutralize the mobile phase while the working detector cell was set at −0.28V for amine detection. A flow of 1 ml/min of monobasic sodium phosphate buffer (pH of 3.6) was used for all separations. With an initial injection of 50 μl of sample, a flow of 1 ml/min allowed for individual isolation of all amines, including the internal standard of DHBA over a 20-min run. The detector response in volts was measured and analyzed by a Water's data module. The area under the curve was determined and compared with standards for quantifying each sample.

The total protein content of each tissue sample was determined from the insoluble pellet obtained from the initial homogenization of the tissue samples. The pellet was resuspended in NaOH, allowed to sit for 24 h and then analyzed using the Bio-Rad Protein Assay method. Protein content was read by a Chemetrics II automated chemistry analyzer.

Dopamine Receptor Assay

Specific binding of ^{3}H-spiroperidol to membranes prepared from brain tissues was assayed by a method described previously.[8] Briefly, fresh brain tissue was homogenized in 10 volumes of a Na-K phosphate buffer (pH of 7.4) with a Polytron homogenizer (3 × 10 sec at setting 5). The homogenate was centrifuged at 40,000 × *g* for 20 min and the pellet was resuspended in phosphate buffer and centrifuged again at 40,000 × *g* for 20 min. The resulting pellet was resuspended in the buffer. Of this homogenate, 100 μl (containing approximately 100 μg of protein) was added to each of a set of test tubes containing various concentrations of ^{3}H-spiroperidol (New England Nuclear; specific activity 25 Ci/mmol) in phosphate buffer. Five ligand concentrations varying from 50–800 pM were used. Binding with each concentration was run in triplicate. Nonspecific binding was determined by addition of 1 μM of d-butaclamol to a similar set of sample tubes. The test tubes and their contents (total volume of 10 ml) were incubated at 37°C for 30 min in a water bath. The incubate was then filtered through a glass filter (Whatman GF/B) under suction. Radioactivity trapped in the filter was measured by scintillation-counting technique with an Omnifluor-toluene scintillant at 40% counting efficiency. Protein concentration of the final tissue homogenate was determined by the method of Lowry et al.[9] using bovine serum albumin as standards. Concentration (fm/mg protein) and affinity (pM) of the receptors were determined by Scatchard analysis.

Data Analysis

Data analysis was approached in two ways. First, formal statistical analyses were carried out to test for associations between ethanol exposure (MPPEC) and each developmental and neurological outcome measure. The χ^2 test and the binomial test were used to assess categorical measures of pregnancy and neurological outcome. Analysis of variance was used to compare mean outcome scores between exposure cohorts. Standard multiple regression analysis was used to determine whether maternal ethanol exposure during pregnancy explained a significant proportion of the variance in infant striatal dopamine, DOPAC, and dopamine receptor concentrations, after controlling for confounding and interaction with secondary variables (ketamine, exposure, and age). Backwards and stepwise variable selection was performed with *F*-to-enter set at $p = 0.05$ and *F*-to-remove set at $p = 0.10$. Interaction terms between maternal ethanol exposure (MPPEC) and each secondary variable were computed. Each interaction term was allowed to enter the equation containing the interaction component variables by stepwise selection to determine if ketamine or age significantly modified the effect of maternal ethanol exposure on each dependent variable. Scatter diagrams of MPPEC^2 terms were entered into each equation and retained if they explained a significant increase in variation, beyond that explained by the straight-line model. Small sample sizes necessarily limit inferences that can be drawn from these assessments.

In addition to the formal statistical assessments that were described above, a more descriptive approach was also employed to identify individual animals that showed evidence of developmental impairment,

and to identify patterns of effect across all infants as they relate to the level and timing of intra-uterine ethanol exposure. For each animal, the raw score for each outcome measure was transformed into a normally standardized z-score based on the corresponding mean and standard deviation in the unexposed animals. Affected animals were defined as those infants with z-scores >2 standard deviations. The results of this assessment are presented in Fig. 1 as an extension of the figure as previously published.[5]

RESULTS

Neuropathology

A small but statistically significant decrease in brain volume (3%) was detected in the 12 animals who received delayed or full-gestational exposures to MPPECs at or above 140 mg/dl. True microcephaly was only noted in one animal exposed to an MPPEC of 540 mg/dl administered after the 5th week of gestation.[6] No gross malformations were found in any brain specimen. No abnormalities of cerebral cortices or nuclei, glia, or neurons were confirmed by observation of the brain samples prepared for review with the light microscope.

Ocular Pathology

Tortuosity of retinal blood vessels, a noted feature in humans with FAS, was not observed in this series of nonhuman primates. Three of the animals showed bilateral microphthalmia (globe diameters of 17 mm or less in all three meridia), including one animal whose mother was exposed to 0.6 g/kg ethanol, one animal whose mother was exposed to 1.2 g/kg ethanol and one from the delayed dose group (Fig. 1). Microcornea (both diameters 9 mm or less) was observed only in the left eye of animal number 19, an infant whose mother was exposed to 1.2 g/kg ethanol. Mild ganglion cell loss was also noted in the left eye. The right eye of this animal had a normal sized cornea (11 × 10 mm), but had marked ganglion cell loss.

The mean diameters for each meridia across the left and right globes of the five control animals were 18.2 ± 0.6, 18.0 ± 0.7, and 18.6 ± 0.5. Three of these animals had normal ganglion cell numbers while the other two had mildly reduced ganglion cell numbers bilaterally. Marked loss of retinal ganglion cells was observed in five of the 26 ethanol-exposed animals, including one from the 0.3 g/kg ethanol exposed group, one from the 1.2 g/kg ethanol exposed group, two from the 1.8 g/kg ethanol exposed group, and one from the delayed dose group. The pattern of marked ganglion cell loss was always found in only one retina with mild ganglion cell loss in the opposite retina. Mild ganglion cell loss was found in all of the other ethanol exposed animals. In the majority (19) of these monkeys, the mild ganglion cell loss was bilateral; in the other two, mild ganglion cell loss was unilateral and the opposite retina had normal ganglion cell counts. The frequency of mild to marked ganglion cell loss in the ethanol-exposed animals (100%) was significantly greater than the frequency of ganglion cell loss in the controls (40%, $\chi^2 = 11.1$, $p = .0009$ with Yates correction).

Dose Pattern	Animal I.D.	Cohort	Etoh (g/kg)	MPPEC (mg/dl)	Neurologic Dysmorphic	Microphthalmia Retina gang. loss	Suck response	Obj. perm	WGTA	Visual recog.	Motor dev.	Facial Movmt	Weight	Head Circum.
FULL	1	I	0	0	○○	○○	○○			○	○○		○○	○○
GEST.	2		0	0	○○	○○	○	○	○	○	○○		○○	○○
EXPOS.	3		0	0	○○	○○			○	○	○		○	○○
	4		0	0	○○	○○	○	○	○	○	○		○	○○
	5		0	0	○○	○○	○	○	○	○	○		○○	○○
	6	II	0.3	18	○○	○○		○		○	○		○	○○
	7		0.3	23	○○	○○	○	○		○	◑		○	○○
	8		0.3	24	○○	○○	○	○	◑	○	○			○○
	9		0.3	25	○○	○○	○	○	◑	○	○		○	○○
	10		0.3	25	○○	○●	○	○	○	○	○		○○	○○
	11		0.3	25	○○	○○	○							○○
	12		0.3	26	○○	○○	○	○	○	○	○			○○
	13	III	0.6	51	○○	●○	○	○		○	◑		○	○○
	14		0.6	51	○○	○○	○	○	○	○			○	○○
	15		0.6	54	○○	○○	○							○○
	16		0.6	67	○○	○○	○	○		○	○		○○	○○
	17		0.6	67	○○	○○	○	○	○	○	○		○○	○○
	18		0.6	70	○○	○○	○	○	◑	○	○		○○	○○
	19	IV	1.2	115	●○	●○	○	○	○	○	○		○○	○○
	20		1.2	117	○○	○○		○		○	○		○○	○○
	21		1.2	124	○○	●●	○	○	○	○	○		○○	○○
	22		1.2	140	○○	○○	○	●	●	○	○		○○	○○
	23		1.2	161	○○	○○	○	○	○	○	○		○◑	○○
	24	V	1.8	189	○○	○●	○	●	◑	○	○		○○	○○
	25		1.8	208	◑●	○●	○	●	●	○				○○
	26		1.8	214	○○	○○	○	○	○	◑	◑		○	○○
	27		1.8	249	○○	○○	●	○	●	●		○		○○
DELAYED	28	VI	2.5	260	◑○	○○	○	○	○	○	○		○○	○○
GEST.	29		2.5	264	○○	○○	○	○	○	○	○		○○	○○
EXPOS.	30		3.3	420	○○	○○	○	○	●	○	◑		○	○○
	31		3.3	431	○○	○○	○		○	○	●		○	○○
	32		3.3	432	○○	○○	○	○	○	○	○		○○	○○
	33		4.1	540	◑○	●●		○		○	●●		●●	●●

Fig. 1. This figure is extended from a previous publication[5] with the addition of two columns depicting ocular pathologic changes. Individual deviations on developmental and growth measures are compared in infant macaques exposed to ethanol in utero and control infants. ●, indicate extreme deviations from control means, while ◑, indicate definite, but less extreme deviation. Only marked retina ganglion cell losses are displayed. Animal 19, who had marked retina ganglion cell loss also had microcornea. Animals 11 and 15 were not available for neuroanalysis; both animals developed serious infectious illnesses and died within the 1st month of life.

Electron-Microscopic Assessment Results

Electron micrographic assessments revealed important anatomical differences among cells from animals exposed to different doses of ethanol during gestation. To assure a focus on neurons, only cells that demonstrated either somatic synapses or multipolar processes were selected for investigation. Cells that were thought to be glial cells were not photographed and were excluded from the evaluation. The normal appearance of a neuron in the caudate nucleus included a round nucleus with peripherally clumped heterochromatin. Organelles in the cytoplasm were evenly distributed and the abundant numbers of mitochondria contained lamellar cristae. Rough endoplasmic reticulum (ER) had a regular array with evenly spaced cisternae

which frequently filled much of the cytoplasm with organized stacks of membranes and polysomes. Intracellular vesicles were usually present.

In contrast, the organelles and cytoplasmic organization of neurons in the nucleus from animals that were exposed to ethanol in utero, had a different appearance (Fig. 2). The cytoplasm of many cells lacked the usual distribution and number of cellular organelles. The most striking differences were in the appearance of the ER. The cisternae of the ER appeared swollen and distended, which resulted often in an oval or round vacuolar appearance rather than flat membranous stacks. The mitochondria showed a variety of structural changes particularly in the loss of cristae, suggestive of a degenerative condition. This is consistent with mitochondrial abnormalities found in rat pups exposed to a 20% ethanol solution during gestation.[10] Vesicles were present in the cytoplasm of these cells, and normal appearing Golgi were present with regularly arranged membranous stacks. However, some areas showed Golgi membranes that did not appear organized but were distended, disordered, and vesiculated. In some of the cells, the nucleus appeared crenated or stellate shaped whereas this appearance was absent in cells from control animals. As seen in Fig. 3, the intracellular dysmorphism score as previously defined, appeared elevated among animals with MPPECs between 214 and 264 mg/dl, including two animals who were not exposed to ethanol until the 5th week of gestation. Animals receiving full gestational exposure to lower doses of ethanol (MPPECs 124–208 mg/dl) and animals receiving delayed exposures to higher levels of ethanol MPPECs 420–540 mg/dl) had dysmorphism scores similar to those of control animals. Assessments of the cells in other brain areas are not yet completed.

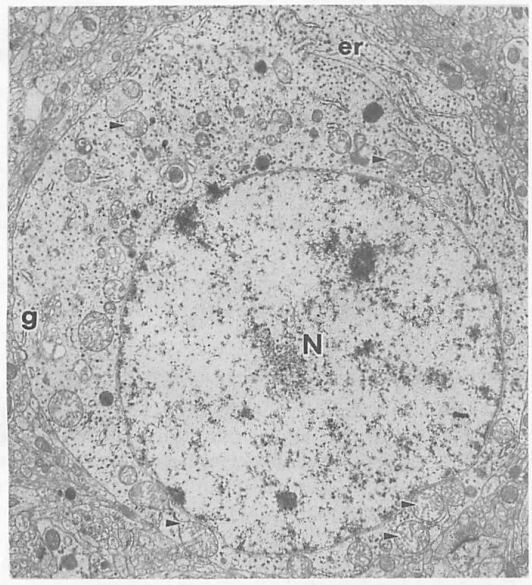

Fig. 2. Photograph of a neuron from the caudate nucleus of a monkey whose mother was exposed weekly to 1.8 g/kg of ethanol throughout pregnancy (magnification ×4,000). Note the relatively sparse amount of peripheral heterochromatin in the nucleus (N). The cytoplasm contains abundant numbers of organelles in this cell, but many of the mitochondria have unorganized cristae (arrow heads). A Golgi body (g) is present, but appears disordered. The cisternae of the rough endoplasmic reticulum (er) is swollen and in some areas it is vacuolar.

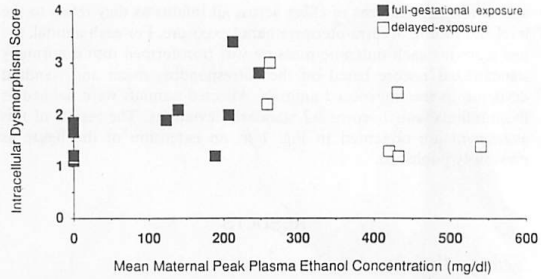

Fig. 3. Infant intracellular dysmorphism score as it relates to maternal MPPEC and timing of ethanol exposure. The intracellular dysmorphism score reflects the extent of intracellular structural alteration observed in the cells of the caudate nucleus. A score of 1 represents no apparent morphological aberration, while scores of 2, 3, 4, and 5 reflect nominal, moderate, substantial, and maximal alteration in structure, respectively. The extent of structural alteration appeared elevated among animals exposed in utero to maternal MPPECs between 214 and 264 mg/dl, including two animals whose ethanol exposure was delayed until the 5th week of gestation.

Neurochemical Analysis

Associations were found between MPPECs dopamine and DOPAC concentrations in the striatal nuclei. Ethanol exposure did not appear to influence dopamine concentrations in other brain areas or epinephrine, norepinephrine, or serotonin concentrations.

Influence of Age and Ketamine Exposure on Striatal Dopamine Concentrations. Dopamine concentrations in the caudate and putamen nuclei were found to vary significantly by animal age and ketamine exposure at the time of death. When final age (days postconception) and ketamine exposure (mg/kg) were regressed on putamen and caudate dopamine concentrations (ng/mg protein), age explained 38% of the variance in putamen dopamine concentration [$F(1,28) = 17.4$, $p = 0.003$] and 16% of the variance in caudate dopamine concentration [$F(1,28) = 5.2$, $p = 0.03$]. Ketamine explained an additional 15% of the variance in the putamen [$F(2,27) = 15.2$ $p < 0.0001$], and 19% of the variance in the caudate [$F(2,27) = 7.2$, $p = 0.003$]. Striatal dopamine levels increased with increasing age from 329 to 380 days postconception (Fig. 4). Striatal dopamine concentration decreased with increasing ketamine exposure in what appeared to be a threshold effect at exposures ≥21 mg/kg (Fig. 5). Thirty of the 31 animals were entered into this regression analysis; one subject had an invalid dopamine assay.

The mean total ketamine doses across all infants was 19 ± 9 mg/kg with a range of 9 to 43 mg/kg. The mean

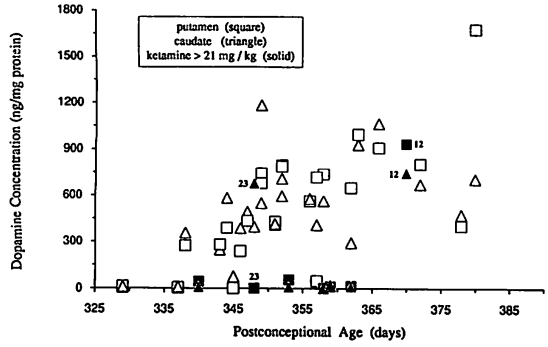

Fig. 4. Striatal dopamine as it relates to postconceptual age. The cuadate and putamen dopamine concentrations (ng/mg protein) for each animal are presented as they relate to postconceptual age at killing. Striatal dopamine concentration increased with increasing age from 329 to 380 days postconception. Total ketamine exposures ≥21 mg/kg are associated with markedly reduced dopamine concentrations. Animal No. 12 was the only animal to receive a high total ketamine exposure that was delivered in a series of small doses.

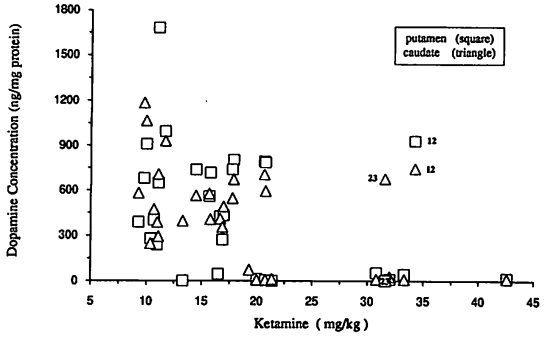

Fig. 5. Striatal dopamine as it relates to ketamine exposure. The caudate and putamen dopamine concentrations (ng/mg protein) for each animal are presented as they relate to total ketamine exposure at the time of killing. Striatal dopamine concentrations decreased with increasing total ketamine exposure in what appeared to be a threshold effect at exposures ≥21 mg/kg. Animal No. 12 was the only animal to receive a high total ketamine exposure that was delivered in a series of small doses.

caudate and putamen dopamine concentrations across all subjects in both pattern groups were 439 and 452 ng/mg protein, respectively; the medians were 473 and 400, respectively. Seven infants received total ketamine doses ≥21 mg/kg. Of these seven infants, five (71%) had caudate dopamine levels below 50 ng/mg protein and six (85%) had putamen dopamine levels below 50 ng/mg protein. Animal 12 was the sole subject with a total ketamine exposure above 21 mg/kg and measureable dopamine concentrations in both caudate and putamen. It should be noted that this animal had a unique ketamine exposure. While its total ketamine dose was 34 mg/kg, the drug had been delivered in a series of small aliquots over 30 min. Of the 23 infants with ketamine exposures less than 21 mg/kg, only four (17%) had putamen dopamine concentrations below 50 ng/mg protein and only two (8%) had caudate dopamine concentrations below 50 ng/mg protein. Ketamine exposure was unrelated to age, the level of maternal ethanol exposure or the timing of ethanol exposure.

To simplify the interpretation of the dopamine assay data, the animals were divided into two groups, those exposed to ethanol weekly througout gestation ($n = 25$) and those whose weekly ethanol exposure was delayed until the 5th week of gestation ($n = 6$).

Striatal Dopamine, DOPAC, and Dopamine Receptor Concentrations among Animals Exposed to Ethanol throughout Gestation. Among the animals exposed to ethanol throughout gestation, MPPEC explained 13% of the variance in putamen dopamine concentration after adjustment for the effect of age and ketamine exposure [$F(5,19) = 10.5$, $p = 0.0001$] (Table 1). MPPEC, expressed as a second order polynomial, provided the best fit of the data. Putamen dopamine increased with increasing MPPEC, increased with increasing age and decreased with increasing ketamine exposure. There was a significant interaction between MPPEC and final age. This interaction reflected the unequal age distribution at the time of death along the continuum of MPPEC. The age range was much broader among the animals exposed to MPPECs ≤100 mg/dl (329–380 days) compared with animals exposed to MPPECs >100 mg/dl (348–362 days). MPPEC, final age and ketamine exposure, together explained 74% of the variance in putamen dopamine concentration.

Similar results were found when MPPEC, final age, and ketamine exposure were regressed on caudate dopamine levels among the infants exposed to ethanol throughout gestation (Table 1). Caudate dopamine concentrations increased linearly with increasing MPPEC. MPPEC explained 17% of the variance in caudate dopamine levels after adjustment for age and ketamine exposure [$F(4,19) = 6.4$, $p = 0.002$]. Caudate dopamine levels increased with increasing age and decreased with increasing ketamine exposure. Once again, there was a significant interaction between MPPEC and age, reflecting the unequal distribution of age with increasing MPPEC. MPPEC, age, and ketamine exposure explained 57% of the variance in caudate dopamine levels.

DOPAC concentrations correlated significantly with dopamine concentrations in the putamen (Pearson correlation coefficient = 0.45, $p = 0.03$). A much weaker correlation between dopamine and DOPAC was found in the caudate (Pearson correlation coefficient = 0.32, $p = 0.12$). Ketamine exposure and final age did not appear to influence the DOPAC concentrations. Adequate assays for DOPAC concentration were only obtained in 17 of 25 full gestation exposed subjects.

Dopamine receptor levels (fm/mg protein) in the caudate increased gradually with increasing MPPEC (0–250 mg/dl) and increasing age (329–380 days) (Table 2). MPPEC explained 22% of the variance in caudate dopamine receptor levels. Final age explained an additional 32% of the variance [$F(3,19) = 11.3$, $p = 0.0002$]. There

Table 1. MPPEC (0–249 mg/dl), Final Age and Ketamine Exposure Regressed on Putamen and Caudate Dopamine Concentrations among Animals Exposed Weekly to Ethanol throughout Gestation

Independent variables	B	SE of B	Beta	*F*	Signif *F*
Dependent variable: Putamen dopamine concentration (ng/mg protein)					
$MPPEC_2$	99.2	41.2	17.3	5.8	0.026
MPPEC	.03	.01	1.1	6.8	0.02
Age	32.5	5.9	0.9	30.3	0.0000
Ketamine	−15.9	6.1	−0.3	6.8	0.02
Age * MPPEC	−0.3	0.1	−18.3	6.8	0.02
(constant)	−10635.2	2098.4		26.0	0.0001
$F(5,19) = 10.5, p = 0.001$ $R^2 = 0.74$					
Dependent variable: Caudate dopamine concentration (ng/mg protein)					
MPPEC	101.6	36.5	24.9	7.8	0.01
Age	21.4	5.3	0.8	16.0	0.0007
Ketamine	−14.4	5.3	−0.4	7.3	0.01
Age * MPPEC	−0.3	0.1	−24.8	7.8	0.01
(constant)	−6929.4	1889.8		13.7	0.002
$F(4,19) = 6.4, p = 0.002$ $R^2 = 0.57$					

Table 2. MPPEC (0–249 mg/dl), Final Age and Ketamine Exposure Regressed on Caudate and Putamen Dopamine Receptor Concentrations among Animals Exposed Weekly to Ethanol throughout Gestation

Independent variables	B	Beta In	SE of B	Beta	*F*	Signif *F*
Dependent variable: Putamen dopamine receptor concentration (fm/mg protein)						
MPPEC		−0.27			1.6	0.21
Age		0.27			1.7	0.31
Ketamine		0.05			0.1	0.81
Age * ketamine		0.08			0.1	0.73
Age * MPPEC		−0.27			1.7	0.21
Ket * MPPEC		−0.12			0.3	0.59
Dependent variable: Caudate dopamine receptor concentration (fm/mg protein)						
MPPEC	62.8		18.3	25.3	11.6	0.003
Age	13.9		2.6	1.0	28.1	0.0000
Age * MPPEC	−0.2		0.05	−25.6	12.3	0.003
(constant)	−4353.9		931.9		21.2	0.0002
$F(3,19) = 11.3, p = 0.0002$ $R^2 = 0.64$						

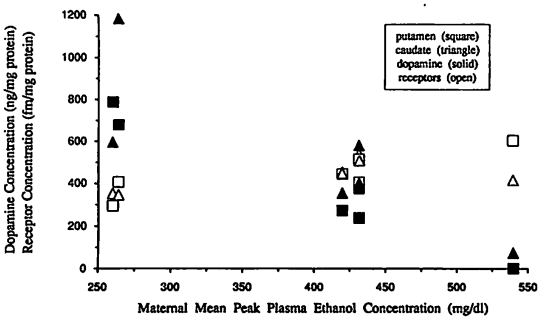

Fig. 6. Striatal dopamine and dopamine receptor concentrations as they relate to maternal MPPEC among the delayed-dose infants. Striatal dopamine and dopamine receptor concentrations for the delayed-dose infants are presented as they relate to MPPEC. Dopamine levels appear to be decreasing with increasing MPPEC, while dopamine receptor levels appears to be increasing.

was a significant interaction between age and MPPEC. Ketamine exposure appeared to have no influence on receptor levels. In contrast, MPPEC, age and ketamine exposure appeared to have no influence on putamen dopamine receptor levels (Table 2).

Striatal Dopamine, DOPAC and Dopamine Receptor Concentrations among Delayed-Dose Animals. Among the six high-dose animals (MPPEC = 260–540 mg/dl) whose ethanol exposure was delayed until the 5th week of gestation, putamen and caudate dopamine levels decreased linearly with increasing MPPEC (Fig. 6 and Table 3). MPPEC explained 95% of the variance in putamen dopamine [$F(1,4) = 83.1$, $p = 0.0008$) and 68% of the variance in caudate dopamine [$F(1,4) = 8.7$, $p = 0.04$]. The putamen and caudate dopamine concentrations for the two delayed-dose animals exposed to MPPECs of 260–264 mg/dl were comparable of 189 to 249 mg/dl *throughout* gestation. Striatal dopamine levels were not influenced by ketamine exposure (9–20 mg/kg) or final age (338–353 days) in the delayed-dose group. This lack of effect is probably due to the narrow range of each of these parameters within this group.

Putamen and caudate dopamine receptor levels (fm/mg protein) appeared to increase with increasing MPPEC among the six delayed-dose animals (Fig. 6 and Table 4). MPPEC explained 74% of the variance in putamen dopamine receptor levels [$F(1,4) = 11.1$, $p = 0.029$] and 88%

Table 3. MPPEC (260–540 mg/dl), Final Age and Ketamine Exposure Regressed on Putamen and Caudate Dopamine Concentrations among Animals whose Weekly Exposure to Ethanol Was Delayed until the 5th Week of Gestation

Independent variable	B	SE of B	Beta	F	Signif F
Dependent variable: putamen dopamine concentration (ng/mg protein)					
MPPEC	−2.6	0.3	−1.0	82.8	<0.0008
(constant)	1419.2	116.1		148.8	0.0003
$F(1,4) = 83.1, p < 0.0000$ $R^2 = 0.95$					
Dependent variable: caudate dopamine concentration (ng/mg protein)					
MPPEC	−2.8	0.9	−0.8	8.4	0.04
(constant)	1632.2	386.5		17.6	0.01
$F(1,4) = 8.7, p = 0.04$ $R^2 = 0.68$					

Table 4. MPPEC (260–540 mg/dl), Final Age and Ketamine Exposure Regressed on Putamen and Caudate Dopamine Receptor Concentrations among Animals Whose Weekly Exposure to Ethanol Was Delayed until the 5th Week of Gestation

Independent variable	B	SE of B	Beta	F	Signif F
Dependent variable: putamen dopamine receptor concentration (fm/mg protein)					
MPPEC	0.8	0.3	0.9	10.9	0.29
(constant)	117.6	101.4		1.4	0.300
$F(1,4) = 11.1, p = 0.029$ $R^2 = 0.74$					
Dependent variable: caudate dopamine receptor concentration (fm/mg protein)					
MPPEC	5.0	1.3	6.8	13.7	0.03
$MPPEC^2$	−0.006	0.001	−6.2	11.6	0.04
(constant)	−551.7	243/7		5.3	0.10
$F(2,3) = 10.6, p = 0.04$ $R^2 = 0.86$					

of the variance in caudate dopamine receptor levels [$F(2,3) = 10.6, p = 0.04$]. MPPEC, expressed as a second-order polynomial, provided the best fit of the caudate receptor data. Age and ketamine exposure appeared to have no influence on the striatal dopamine receptor levels in the delayed-dose animals.

DOPAC concentrations were available on five of the six delayed-dose animals. There was no significant correlation between DOPAC and dopamine concentrations in either the putamen or caudate. Scatter plots of DOPAC versus dopamine did, however, suggest that DOPAC concentrations were paralleling dopamine levels in the caudate.

DISCUSSION

Weekly exposure to ethanol during gestation, even very heavy exposure, did not produce obvious structural disorganization of the central nervous system. A number of subtle abnormalities were detected, which could be important clues towards the final delineation of ethanol's effect on the structure and function of the developing brain. The most striking pathologic abnormalities was found in the eyes. Several of the ethanol-exposed animals had ocular anomalies comparable with those recognized in humans with FAS,[11] including asymmetrical microphthalmia in three animals, microcornea in one animal, and marked loss of retinal ganglion cells in five animals. The frequency of ocular abnormalities appeared to increase with increasing MPPEC among both the delayed and full-gestational exposure animals. Ocular abnormalities rarely occurred in both eyes. The discrepancy between eyes may suggest that relatively small windows in gestational time may exist in primate eyes for expression of the deleterious effects of ethanol. This would be analogous to the situation reported in a mouse model for ocular anomalies in FAS.[12] Microcornea and marked retinal ganglion cell loss were observed together in animal 19, exposed to the 1.2 g/kg dose throughout gestation, while microphthalmia and marked retinal ganglion cell loss were only observed together in animal 33 who had been exposed to the very highest level of ethanol exposure after the 5th week of gestation.

Morphometric counts of retinal ganglion cells have not been performed to our knowledge in humans with FAS. All of the animals exposed to ethanol showed at least mild decrease in ganglion cell numbers. This agrees with observations in rats exposed to intrauterine ethanol where mild decreases in numbers of myelinated axons were found in the optic nerve.[13] Although these ganglion cell losses were often mild, there was a very significant difference in frequency of ganglion cell loss between controls and ethanol exposed animals. The reason for marked asymmetry of the counts between the eyes of the same animals is not known.

The loss of retinal ganglion cells should have been associated with laminar abnormalities in the lateral geniculate and the calcarine cortex. Abnormalities in those brain areas were not positively identified but neither were they fully excluded. The technique of single section sampling of brain areas was selected in this project as a

reasonable and cost effective screening procedure. Obvious structural abnormalities were anticipated in some animals as previously reported in humans and nonhuman primates.[14,15] Unfortunately, such a sampling technique cannot reliably distinguish a true subtle defect in laminar structure from an artifact in the angle of section. Serial sectioning of brain areas at high risk for teratogenic alteration should be done in the future if studies of this type are repeated.

We were surprised to find that very high ketamine exposures were associated with decreased dopamine levels. This ketamine effect was independent of prenatal alcohol exposure and age. What appeared to be a "threshold effect" at ketamine doses ≥21 mg/kg contrasts with the results presented by Sung et al. (1973) and Ylitalo et al. (1976),[16,17] who both assessed brain dopamine concentrations following ketamine injection in rats. Ylitalo noted that after injection of 100 mg/kg ketamine intraperitoneally, brain dopamine content was unchanged at 15 min, 1 hr, and five hr after administration. The striatal HVA content, however, was increased by about 55% ($p < 0.05$) at 15 min and 1 hr after administration, suggesting an increased turnover of dopamine. Sung[16] also reported a lack of change in brain dopamine concentrations at 1, 2, 4, and 6 hr after administration of 20 and 40 mg/kg ketamine in rats. He did note, however, that ketamine did affect the rate of decline of dopamine after inhibition of tyrosine hydroxylase with DL-a-methyltyrosine methyl ester hydrochloride (aMT) suggesting that ketamine may increase the rate of dopamine synthesis. In another study using a primate species (*C. aethiops*), Bacopoulos noted that the concentration of dopamine metabolites in brain regions was not altered by doses of 10 mg/kg ketamine.[18] The influence of high ketamine exposure on striatal dopamine concentrations, observed in this study, warrants further investigation.

The striatum receives its dense dopaminergic input primarily from the substantia nigra (nigrostriatal system).[19,20] Although secure identification of the neuron cell bodies in the striatum that evidenced degeneration was not possible, it is probable that these cells received dopamine afferents from the substantia nigra.

Among the animals exposed to MPPECs between 0 and 249 mg/dl throughout gestation, striatal dopamine concentrations appeared to *increase* with increasing MPPEC. In contrast, striatal dopamine concentrations *decreased* with increasing ethanol exposure among the animals in the delayed gestation exposure cohort. In the striata of the delayed gestation exposure cohort, a reciprocal relationship was observed between the concentrations of dopamine and that of dopamine receptors. In the other groups, caudate dopamine receptors increased with increasing dopamine concentrations, but putamen dopamine receptors did not vary at all with dopamine concentration. One might also expect that DOPAC concentration would parallel dopamine concentration. This was found to be the case in putamen measurements in the full gestation exposure cohorts, but not in the caudate. DOPAC did not vary with dopamine exposure in the striata of delayed gestation exposed animals either. No easy explanation for these disparate observations is forthcoming.

It was not anticipated that a teratogen like ethanol would produce abnormally high levels of a neurochemical like dopamine when exposure occurred in one dosing paradigm and abnormally low levels of the same neurochemical when exposure occurred in a different dosing paradigm. Further study into the validity of this observation is necessary. If this observation is confirmed, it may help to explain the clinical diversity in degree and types of behavior and cognitive deficit found in children with alcohol-related birth defects.

In conclusion, this study emphasizes that normal physical features and only subtle neuroanatomic and neurochemical alterations may be associated with abnormal behavioral development in nonhuman primates exposed to ethanol in utero. By extension, the work supports the position that human infants exposed to ethanol in utero cannot safely be said to be "unaffected" because of a normal appearance, normal head circumference, or normal brain imaging study. Further work in delineating infant teratogenic risk from moderate and intermittent ethanol exposure is still vitally needed for maternal counseling and development of appropriate risk categories for infant follow-up.

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TERATOLOGY 44:29–36 (1991)

Holoprosencephaly in a Fetal Macaque *(Macaca nemestrina)* Following Weekly Exposure to Ethanol

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ABSTRACT Previous studies in rodents have indicated that the facial changes of fetal alcohol syndrome (FAS) closely resemble those of a mild form of holoprosencephaly. In order to examine this relationship in non-human primates, we evaluated a 133-day gestation macaque *(Macaca nemestrina)* with holoprosencephaly, median cleft lip and palate, and encephalocele. The mother had been given ethanol once per week (1.8 g/kg body weight) from weeks 2 to 19 postconception. Diagnosis of holoprosencephaly was made following ultrasound evaluation for polyhydramnios and delivery of the female fetus by caesarean section. Another fetus of identical age was delivered by caesarean section for use as a control. Both fetuses were studied by anthropometric, gross, radiographic, and histologic techniques. In the fetus exposed to alcohol, no extracranial anomalies were identified and the karyotype was normal. The brain was micrencephalic, with absent olfactory bulbs, tracts, optic nerves and chiasma, fused frontal lobes, and a single, dilated lateral ventricle; a parietooccipital encephalocele consisted of thin, dysplastic cortex bordering the ventricle; the cerebellum was dysplastic and superiorly displaced. Within the craniofacial complex, anophthalmia was bilateral; premaxillary components were absent, palatal shelves separate, the maxillae closeset, and the ethmoid bone small and deformed. Most of these defects are similar to those encountered in humans with holoprosencephaly and support the hypothesis of shared etiologic and pathogenetic relations between the facial anomalies of fetal alcohol syndrome and holoprosencephaly.

Studies in mice indicate that the changes of fetal alcohol syndrome (FAS) closely resemble those associated with mild forms of holoprosencephaly (Sulik and Johnston, '82; Sulik et al., '84). Several authors have indicated that the frontonasal anomalies in human FAS may also be seen as part of the facial dysmorphology associated with holoprosencephaly (Pfeiffer et al., '79; Jellinger et al., '81; Majewski, '81; Ronen and Andrews, '87). While no consensus has been achieved, the issue remains an important one. To identify alcohol as an etiologic agent responsible for holoprosencephaly in humans would broaden the teratogenic range of alcohol and possibly further the understanding of mechanisms responsible for the development of holoprosencephaly.

CASE REPORT

As part of a continuing study of the teratogenic effect of binge drinking in different periods of gestation, 28 pregnant pigtail macaques *(M. nemestrina)* were randomized to one of four cohorts. Three cohorts received ethanol once per week (1.8 g/kg body weight by nasogastric tube) for the first 3 or 6 weeks of gestation, or for the complete 24-week gestation; the fourth cohort received a sucrose solution that was isocaloric and isovolemic to the ethanol solution. One mother

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TABLE 1. Comparison of somatic and craniofacial features[1]

Feature	Exposed	Control
Gestational age (days)	133	133
Sex	Female	Male
Body weight (g)	218	292
Crown-rump length (mm)	135	160
Foot length (mm)	53	60
Head length (mm)	53	63
Head width (mm)	40	49
Outer orbital distance (mm)	23	30
Inner canthal distance (mm)	6	7
Brain weight (g)	24	57

[1]Measures obtained after formalin fixation. See text for discussion.

in the 24-week exposure cohort developed polyhydramnios; her peak plasma ethanol concentration was 211 mg/dl, and she had previously given birth to three normal infants. Ultrasound examination in the 18th week demonstrated maldevelopment in the brain of the fetus. Caesarean section was performed at 133 days gestation and the female fetus died shortly thereafter. A karyotype was subsequently normal. An untreated male fetus of identical gestation (and different mother) was later delivered by caesarean section and used as a control. Both animals were studied by anthropometric, gross, radiographic, and histologic techniques.

RESULTS

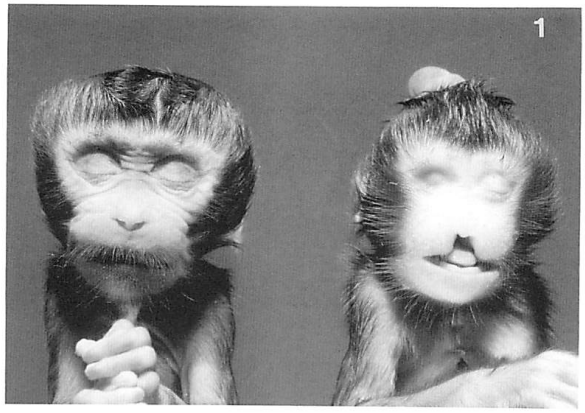
The fetus exposed to alcohol was smaller than the control animal, as evidenced by decreases in body weight, crown-rump length, and foot length; the head was considerably smaller in length and biparietal width, and outer orbital and inner canthal distances were reduced (Table 1). A median cleft lip and palate were evident, the snout was flattened and eyelids asymmetric, and a parietooccipital encephalocele protruded through the calvaria (Figs. 1, 2). Radiographically, the premaxilla and upper central and lateral incisors were absent; the palate was cleft and the ethmoid complex small and deformed; and the medial orbital walls were intact (Fig. 3). A gross dissection of facial tissues revealed absence of the orbicularis oris in the region of the cleft. Histologic examination of the craniofacial complex confirmed the radiographic findings and in addition revealed bilateral anophthalmia; eyelids, conjunctiva, extraocular muscles, glands, and nerves were well-formed and focally edematous (Fig. 4).

The brain of the treated animal was severely microencephalic (Figs. 5, 6; Table 1). The frontal poles were fused and an encephalocele protruded from the convexity; olfactory bulbs, tracts, optic nerves, and chiasma were absent; and the lateral ventricles existed as a large, confluent space which extended to and occasionally ruptured through the cortical surface. In the left temporal pole, a distended subarachnoid space bordered areas of nodular cerebral dysplasia and cortical thinning. A defect in occipital cortex was apparent; the cerebellum and brainstem were displaced superiorly. Microscopic examination showed severe dysplasia of cerebrum and cerebellum.

DISCUSSION

To our knowledge, this is the first report of holoprosencephaly and associated changes of the craniofacial complex in a non-human primate. In addition, only two instances of naturally occurring cleft lip and palate in macaques are known (Hendrickx and Prahalada, '86). One pigtail macaque *(M. nemestrina)* was born at the Regional Primate Center, Seattle, WA, in 1983, and although retarded, lived nearly 3 years; the animal had a novel karyotype (42,XY/43,XY, + variable), termed *mosaic variegated trisomy* (Vigfusson et al., '86). A rhesus monkey *(M. mulatta)* with cleft lip and palate was described by Swindler and Merrill ('71) and likewise survived a number of years, serving as a breeder at the Primate Field Station in Medical Lake, WA. Autopsy information was unavailable for the two animals, but we surmise that neither had holoprosencephaly—at least of the severe variety—because of the length of survival and reasonably intact neurologic function.

The present case manifests a rare form of holoprosencephaly associated with anophthalmia, exencephaly (encephalocele), and anterosuperior displacement of posterior fossa tissues. Anophthalmia has been produced experimentally by a variety of agents, including ethanol, and has been reported in some cases of holoprosencephaly (Hogan and Zimmerman, '62; Warkany, '71; Torczynski et al., '77; Cook et al., '87; Siebert et al., '90). The condition represents a failure of optic vesicle outgrowth or, in holoprosencephaly, damage to prechordal mesoderm or anterior neural plate during or possibly prior to gastrulation. The association of holoprosencephaly and exencephaly/anence-



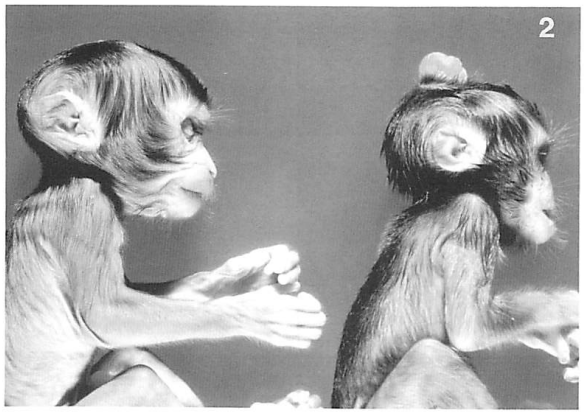


Fig. 1. Frontal view of fetal macaques *(Macaca nemestrina)*. Gestational age of control **(left)** and treated **(right)** animals was 133 days. Median cleft lip and encephalocele are apparent in treated animal.

Fig. 2. Lateral view of control **(left)** and treated **(right)** fetuses. Note encephalocele and flattened snout in the latter animal.

phaly has been reported in a small number of humans, but those individuals had severe deficits in components of the anterior and middle cranial fossae (Lemire et al., '81; Siebert et al., '81). Disruption of posterior fossa tissues probably arose from tethering by the encephalocele during early development. Changes in the craniofacial skeleton of the present case are also considerably milder than those in more severe forms of holoprosencephaly, such as cebocephaly, ethmocephaly, and cyclopia (Kokich et al., '82; Souza et al., '90). Reasons for these differences are unknown, although dosage, time of exposure, nutrition, and genetic predisposition are presumably among the more important factors.

The somatic changes observed in the present case represent a severe reduction in growth that is almost certainly due to the prenatal administration of ethanol. Differences in body size between the treated and

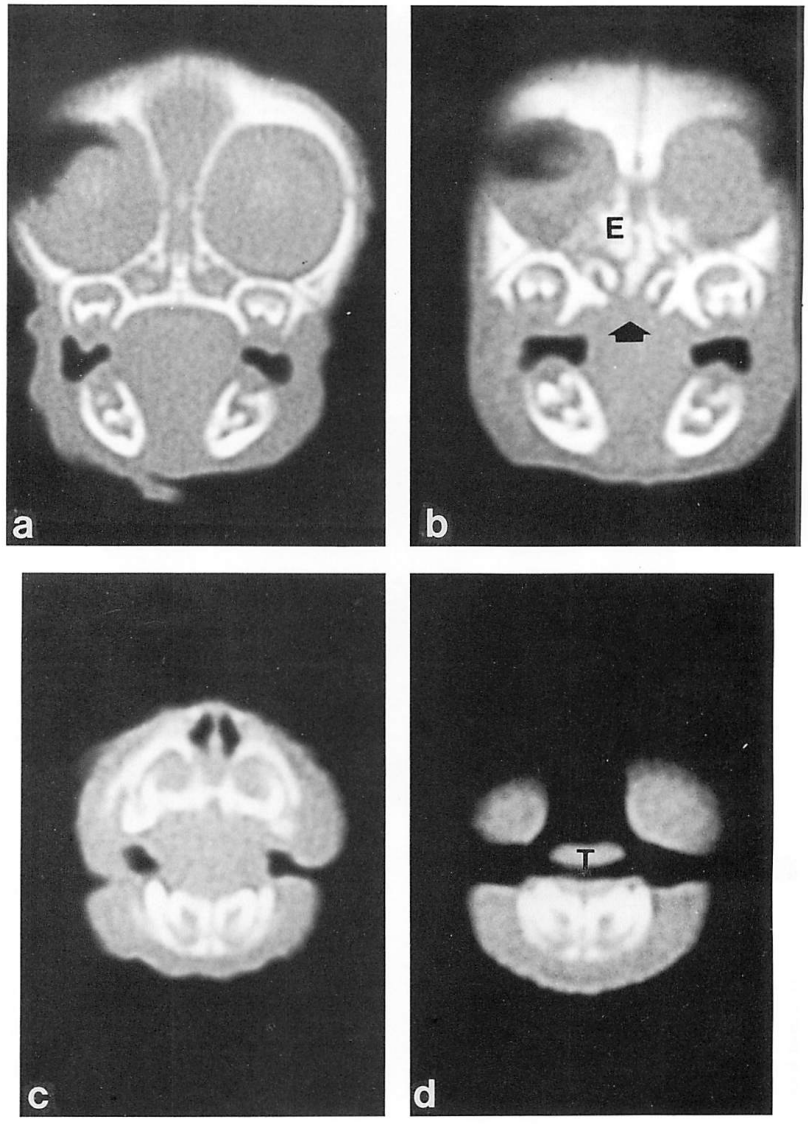


Fig. 3. Computed tomographic scans of control **(a,c)** and treated **(b,d)** fetuses. A dysplastic ethmoid bone (E) and cleft palate (arrow) are visible in b; in d, a median cleft lip, with absent central and lateral incisors, is seen above the tongue (T).

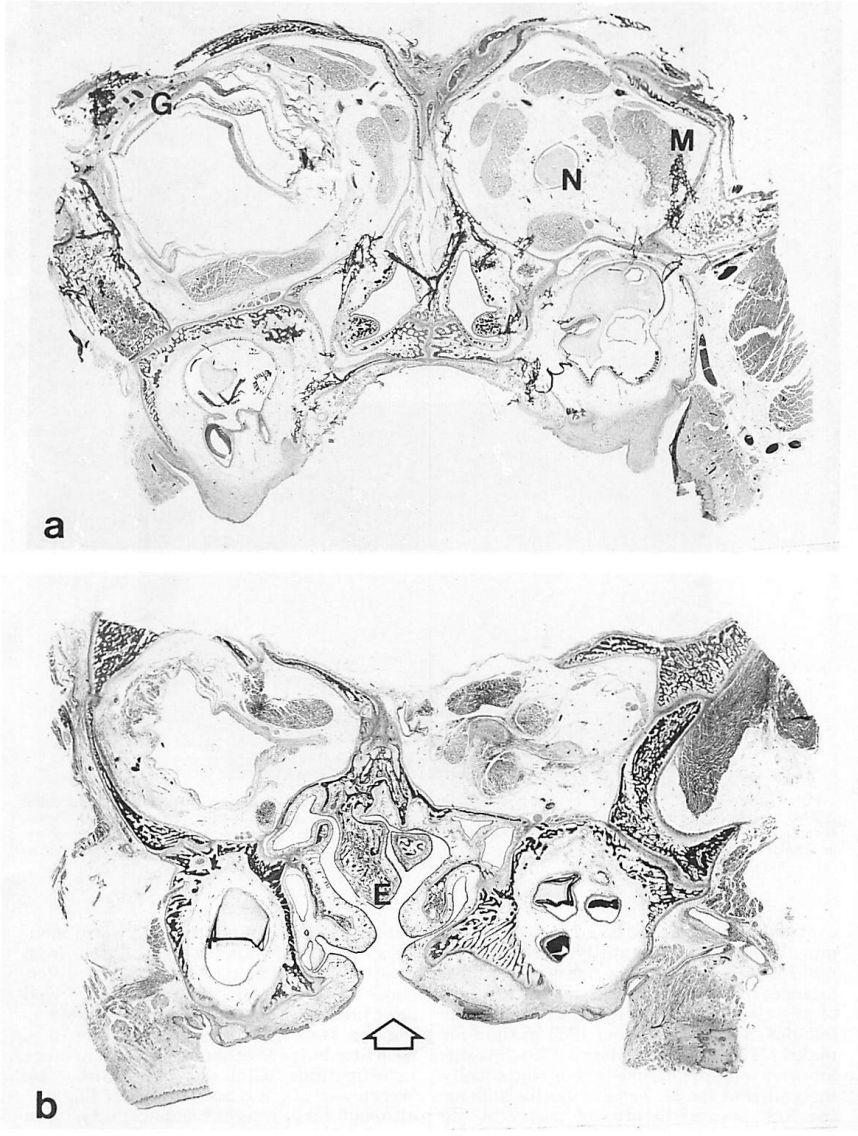


Fig. 4. Microscopic view of the craniofacial complex, sectioned coronally through the orbits, of control (**a**) and treated (**b**) animals. In both, orbital cavities are lined by conjunctiva and contain extraocular muscles (M), nerves (N), and glands (G); serial sections revealed globes in the control animal only. Cleft palate (arrow) and dysplastic ethmoid bone (E) are evident in b. Masson's trichrome stain. Original magnification ×6.

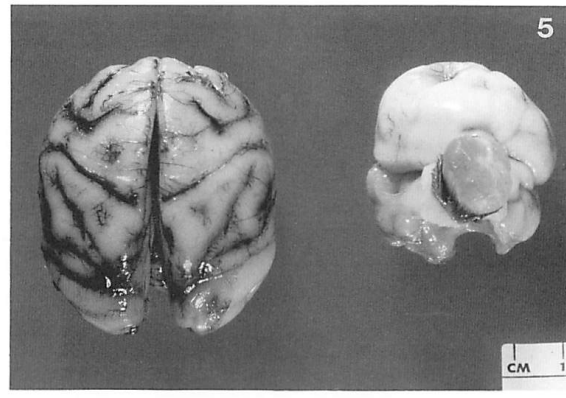


Fig. 5. Superior view of control **(left)** and treated **(right)** brains. Note single frontal lobe (top of figure), encephalocele, and occipital defect in the brain exposed to alcohol.

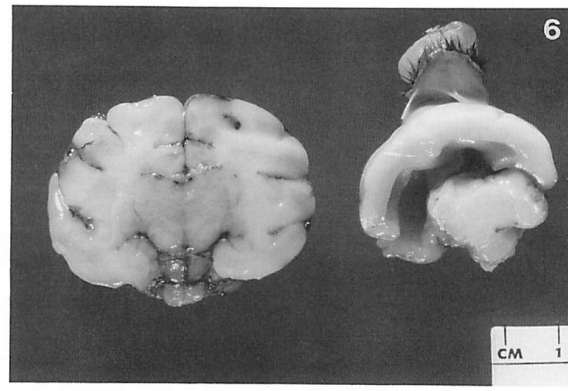


Fig. 6. Coronal sections of control **(left)** and treated **(right)** brains. Encephalocele, fused cerebral cortex, single ventricular cavity, and superiorly displaced cerebellum and brainstem are apparent in the treated brain.

control animals cannot be attributed to sexual dimorphism. Prenatally, male and female *M. nemestrina* show no significant differences in linear measures, and at 133 days of gestation, the expected body weight for females is actually higher (333 g) than for males (313 g) (Newell-Morris, '79). Sex differences remain non-existent or statistically insignificant for *M. nemestrina* throughout the first several months of postnatal life (Sirianni and Swindler, '85). This follows the growth pattern of other old world monkeys, apes, and humans—and differs from most other mammals—in that sex differences fail to become pronounced until well after infancy (Laird, '67; Bogin, '88). Reductions in body and head size at term have been attributed to ethanol exposure in other investigations (Clarren and Smith, '78; Webster et al., '83; Streissguth et al., '85), although birth weight has not always been reduced in macaques exposed to high doses

prenatally (Clarren and Bowden, '82; Bowden et al., '83).

The clinical appearance of the frontonasal complex in mild forms of holoprosencephaly is quite similar to that of FAS. Subtle changes, such as wide inner canthal distance relative to palpebral fissures, short nose relative to midface length, indistinct, elongated philtrum, flat medial midface, and thin vermilion border of the upper lip, as well as the more overt findings of cleft lip and/or palate, are common to both conditions (DeMyer et al., '64; Cohen et al., '71; Jones et al., '73; Clarren and Smith, '78). The midface and anterior cranial base are reduced in both holoprosencephaly and FAS, and associated with choanal narrowing and a hypoplastic ethmoid bone (Johnson, '79; Siebert, '81; Frias et al., '82; Clarren et al., '87). The similarity in phenotypes raises the question of whether the two disorders have a common formative pathway. Put somewhat differently, do subtle anomalies of the frontonasal region (e.g., the facial changes of FAS) represent mild forms of holoprosencephaly? This appears to be the case in the rodent, where the administration of ethanol to pregnant mice produces holoprosencephaly and craniofacial changes equivalent to those in human forms of FAS (Sulik et al., '82; Sulik and Johnston, '83). These observations imply identical or at least overlapping modes of pathogenesis (i.e., Siebert, '83; Siebert et al., '85), although precise mechanisms need to be elucidated.

Previously, diabetes mellitus has been the only non-chromosomal disorder positively associated with holoprosencephaly in humans (Barr et al., '83). Other cases of holoprosencephaly have been associated with maternal alcohol abuse in humans, but only a few have been verified, particularly those reported by Jellinger et al. ('81), Ronen and Andrews ('87), and Bönnemann and Meinecke ('90). In light of the prevalence of FAS, it seems that cases of holoprosencephaly in alcohol-abusing mothers should be more common and easier to document. This is not the case, however. A variety of explanations are possible: It may be that alcohol teratogenesis in non-human primates and humans occurs at highly specific times or dosages. This has been demonstrated in several studies of rodents (Sulik and Johnston, '82; Webster et al., '83; Sulik et al., '85). In addition, Cohen ('89) has pointed out that the comparative rarity of holoprosencephaly in FAS is to be expected, because holoprosencephaly is itself so rare. According to this view, if the prevalence of holoprosencephaly as a fetal alcohol effect were to increase 100 times, it would be observed in only 1 out of every 100–1,000 cases of FAS.

What are the implications of this study for humans? The model demonstrates that a single bolus of alcohol administered weekly initiates teratogenesis in the macaque. In this regard, the experiment mimics binge drinking as it occurs in the human. A dosage of 1.8 g/kg body weight in the macaque is the equivalent of 7 fluid ounces of whiskey, 23 ounces of wine, or 59 ounces of beer in a 55-kg woman (Dubowski, '76). These observations have obvious ramifications for basic scientists, medical workers, and, of course, for society. Despite the accumulating evidence for alcohol teratogenesis, it nevertheless seems unclear if the substance positively causes holoprosencephaly in humans. Both epidemiologic and individual case studies will therefore be necessary to resolve the issue. In the meantime, the appearance of the disorder in rodents and nonhuman primates requires that our suspicions remain high.

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Analysis of Facial Shape in Children Gestationally Exposed to Marijuana, Alcohol, and/or Cocaine

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ABSTRACT. The association between fetal marijuana and/or alcohol exposure and facial features resembling fetal alcohol syndrome was investigated in a sample of 80 children. Standardized lateral and frontal facial photographs were taken of 40 children, 5 to 7 years of age, whose mothers reported frequent use of marijuana during the first trimester of pregnancy and 40 children whose mothers reported no use of marijuana during pregnancy. The marijuana-exposed and unexposed children were group-matched on alcohol exposure prior to and during pregnancy, sex, race, and age at the time of assessment. The photographs were assessed clinically by a study staff dysmorphologist and morphometrically by computerized landmark analysis. Fetal alcohol syndrome-like facial features were not associated with prenatal marijuana exposure in this study sample. No consistent patterns of facial features were identified among the marijuana-exposed group. Maternal consumption of two or more ounces of alcohol per day, on average, in early gestation was found to be associated with fetal alcohol syndrome-like facial features identified both clinically and morphometrically. Cocaine use reported by 13 of the 80 women was independently associated with mild facial dysmorphic features of hypertelorism and midfacial flattening. The results demonstrate the usefulness of this diagnostic technique for quantifying anomalies apparently unique to fetal alcohol syndrome and for targeting clusters of anomalies in new conditions for future evaluation. *Pediatrics* 1992;89:67–77; *marijuana, cocaine, alcohol, facial morphology, fetal alcohol syndrome, fetal exposure.*

Delta-9-tetrahydrocannabinol, the principal psychoactive component of marijuana, is known to cross the placental barrier in humans[1] and therefore has the potential for adversely affecting fetal development. Marijuana is estimated to be used by 1 in every 10 pregnant women. A few studies have presented evidence suggesting an association between fetal marijuana exposure and facial anomalies that resemble those seen in fetal alcohol syndrome (FAS).[2–4] Facial anomalies associated with FAS include a hypoplastic philtrum, thin upper lip, a short nose relative to the midface length, short palpebral fissues, and a flattened maxillary region. The results of these studies suggested that features compatible with FAS may not be specific to alcohol. Small sample sizes, questionable reliability of exposure, other drug use, and/or limited diagnostic sensitivity have precluded drawing firm conclusions from these studies.

In this study, the association between first-trimester fetal marijuana exposure and FAS-like facial anomalies was investigated in photographs of 40 children exposed frequently to marijuana during the first trimester of gestation. The exposure data had been collected prospectively and the association between marijuana and alcohol exposure was effectively eliminated by group-matching. Diagnosis of facial form was assessed clinically by a dysmorphologist and morphometrically by landmark analysis. The sensitivity of the morphometric diagnostic tool has been confirmed in studies of craniofacial malformation[5,6] and has effectively delineated the FAS face in a study sample half the size of the current study population.[4]

METHODS

Subjects

Subjects in the present study were selected from among 1100 mother-infant pairs who participated in a Seattle-based prospective study (1982 through 1987) investigating the effect of maternal diet, drinking, smoking, and marijuana use during lactation on infant growth and development. There were three parts to the original prospective study. First, validity of self-reported alcohol, tobacco, and other drug use and the reliability of the maternal interview process was confirmed.[7,8] Next, descriptive studies were conducted to contrast the dietary habits and alcohol and tobacco use of lactating and nonlactating women.[9–11] And finally, two infant assessment studies were conducted to investigate the influence of alcohol and marijuana use during lactation on infant development at 1 year of age.[12,13]

The subjects' mothers in the original prospective studies were members of Group Health Cooperative of Puget Sound, a Health Maintenance Organization in Seattle, Washington. All prenatal patients receiving care between May 1, 1982, and July 1, 1984, were contracted by the Cooperative in their sixth month of pregnancy regarding possible study participation. Seventy-four percent (5298) of the prenatal patients responded positively and completed a mailed screening questionnaire detailing their alcohol and tobacco use both before and during pregnancy, some dietary information, and their plans to lactate. These patients constituted the screened pool.

A total of 1100 women were selected from the screened pool to participate in one or more of the previous prospective studies. At 6 weeks after delivery, a detailed personal interview was conducted in each woman's home to obtain information on diet, drinking, smoking, and other drug use during pregnancy and the first postpartum month. Additional information on maternal demographics and reproductive history was collected. Similar data were collected in interviews conducted at 3 and 12 months postpartum. Neonatal status (birth weight, birth length, head circumference, gestational age, and Apgar scores at 1 and 5 minutes) was abstracted from the infants' medical records.

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Among the 1100 mothers, 61 reported using marijuana at least once per week during the first trimester of pregnancy and 933 reported no use of marijuana at any time during pregnancy. The children of these 61 mothers made up the exposed cohort in the present study. An equal number of children unexposed to marijuana were selected from the group of 933 by group-matching to the exposed cohort on the following characteristics: reported maternal alcohol consumption during the month prior to pregnancy and during pregnancy and the infant's sex, race, and birth date. Group-matching was performed by stratifying the 933 children simultaneously by sex, age (divided into 6-month groups), race (black, nonblack), and maternal alcohol consumption (AA score: absolute ounces of alcohol per day) both before and during pregnancy, grouped as follows ($AA < 0.05$; $0.05 \leq AA \leq 1.9$; and $2.0 \leq AA \leq 4.0$). Matches were randomly selected from the appropriate groups with the aid of a random number chart. Letters of invitation were sent to the 61 exposed subjects regarding possible study participation. Informed consent was obtained after a full explanation of study procedures. When an exposed subject was successfully located and enrolled in the study, a letter of invitation was sent to the mother of a group-matched unexposed subject. Of the 61 marijuana-exposed mother-child pairs who were eligible for participation in the study, we were able to locate and enroll 40.

Data Collection in the Original Prospective Study

Detailed information on maternal use of alcohol, tobacco, marijuana, cocaine, and other licit and illicit drugs during pregnancy was collected by personal interview at 1 month postpartum. Demographic characteristics and obstetric history were also collected. The interviewers were women of childbearing age, trained to obtain valid and reliable information. Information about maternal use of alcohol in the month prior to conception was collected in a mailed screening questionnaire completed during the sixth month of pregnancy. Use of marijuana and/or cocaine in the month prior to pregnancy was not recorded in this study. Validity of self-reported drug use was confirmed in an earlier pilot investigation of 108 randomly selected postpartum women. Self-reported drug use was compared to laboratory tests of drug levels present in body fluids. The proportion of questionable self-reports ranged from 0% to 3% depending on the drug.[7]

Information about maternal use of marijuana and cocaine was recorded in terms of how often the substance was used (days per week) and how many "joints" or "snorts" were taken per day when the substance was being used. This information was recorded for each trimester. Alcohol consumption was categorized into beer, wine, and liquor and was recorded in terms of frequency of use (days per week), modal quantity, and maximum quantity per drinking occasion in the month prior to conception and during each trimester. These measures were converted to average daily ounces of absolute alcohol ingested per day (AA score).[14]

Assessment of Facial Photographs

Photographic Procedure. An informed consent with a full explanation of study procedures was provided for the parent or guardian and an assent form was provided for the child. Facial form was assessed from standardized frontal and lateral facial photographs. The children were between 5 and 7 years of age at the time of the photograph. A placard with the child's study number and a 2-cm rule was included in each photograph to provide a measure of scale. The children were asked to hold a comfortable pose with their mouths closed while the photographer positioned herself to obtain frontal and lateral pictures with no detectable rotation. The photography session took approximately 20 minutes.

A set of 5 × 7- and 2 × 3-inch, black and white prints were made of each frontal and lateral view. The photographs within each set were printed to scale, within 1 mm accuracy, so that distance measures taken directly from the photographs would be comparable across all the subjects. The larger prints were used for digitization of facial landmarks and measuring distances between landmarks while the smaller prints facilitated the clinical evaluation, permitting scanning of the entire group of photographs at one time.

Clinical Assessment of the Photographs. The photographs of all 80 children were examined and scored by the study staff dysmorphologist (S.K.C.). The photographs were first evaluated for the presence of FAS-like facial features and then for any other pattern of anomaly. Specific attention was given to short palpebral fissues, absent or diminished philtrum, thin upper lip, short nose relative to the midface height, and flattening of the maxillary region. The assessments were performed without knowledge of exposure history. The measures recorded from the 5 × 7 photographs of each child include midface height (entrocanthion to upper lip), nose length (entrocanthion to subnasale), intercanthal distance, palpebral fissure length, philtrum and midface contour (scored as "not," "somewhat," or "definitely flat"), upper lip (scored as "not," "somewhat," or "definitely thin"), and ptsosis (present, absent).

Based on the above measures and the dysmorphologist's overall impression of the child's face, each child was classified into one of the following five groups: (1) no unusual features; (2) unusual features, but not the face of FAS; (3) possible FAS-like face; (4) probable FAS-like face; or (5) definite FAS-like face.

Computerized Morphometric Assessment of the Photographs Using Landmark Analysis. A set of 23 facial landmarks were located and marked on the 5 ×.7 photographs of each child (Fig 1, Table 1). These are the same landmarks that were used in the previous study by Clarren et al.[4] The relative location of the 23 landmarks was entered into a data base with the use of a computer digitizing tablet (MacTablet).

An analysis of facial shape was carried out using methods developed by Bookstein.[15-19] The analysis began with the examination of triangles defined by sets of three landmarks; the mean shapes of these triangles were compared between the exposed and unexposed groups. For example, if a short midface was the facial characteristic of interest, then the triangle resulting from the three facial landmarks 1, 4, and 12 might describe that characteristic (Fig 2). The triangle would be standardized by arbitrarily selecting one edge, for example 1-4, as the baseline and assigning it a standard length of one unit on a Cartesian (x, y) coordinate system (Fig 2). The shape of the triangle would be described by the x and y "shape coordinates" of the third landmark (number 12). The x, y shape coordinates for the triangles of each exposed and unexposed subject could then be displayed in a scatterplot and the mean shape coordinates for each group would be computed as the average (or centroid) of the scatter of shape coordinates within each group (Fig 3). In this hypothetical example, the mean location of landmark 12′ for the exposed group is closer to the baseline 1-4 than the mean location of landmark 12 for the unexposed group. Hotelling's T^2 statistic would be used to determine whether this observed difference in mean shape between the two groups of triangles is significant.

After identifying which triangle(s) had significantly different mean shapes between two groups, a description of how the triangles differed was formulated using tensor analysis. The difference in shape between two triangles can be characterized by a pair of directions at 90°: those for which measured distances show the greatest and least relative charge (expansion or contraction). This pair of directions, drawn to depict the magnitude as well as the direction of shape change, are called "tensor axes" (Fig 4). Tensor

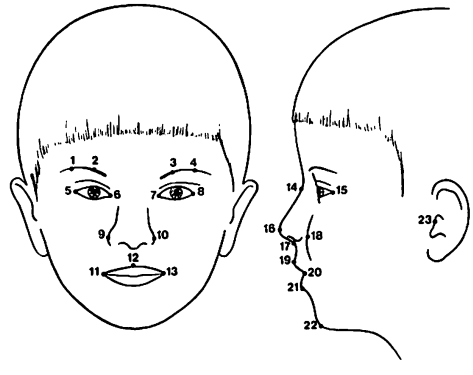


Fig. 1. Twenty-three facial landmarks were identified on the frontal and lateral photographs of each child.[4] The coordinates associated with each landmark were entered into a data base by computer digitization. The landmark definitions are presented in Table 1.

TABLE 1. Definition of the Facial Landmarks*

Landmark	Common Name	Definition
		Frontal view
1, 4		Intersection of the eyebrow curve and a vertical line through the exocanthion
2, 3		Intersection of the eyebrow curve and a vertical line through the midpoint of the palpebral fissure
5, 8	Exocanthion	Lateral intersection of upper and lower eyelids
6, 7	Entrocanthion	Medial intersection of upper and lower eyelids
9, 10		Most lateral points on alar curvature
11, 13	Cheilon	Lateral intersection of upper and lower vermilion
12		Midpoint of upper vermilion border
		Lateral view
14	Nasion	Point of maximum curvature over nasal bridge
15	Exocanthion	Lateral intersection of upper and lower eyelids
16	Pronasale	Point of maximum curvature over nasal tip
17	Subnasale	Intersection of columella and philtrum
18		Point of maximum curvature of soft tissue fold from zygoma
19		Border of upper vermilion and philtrum
20	Cheilon	Lateral intersection of upper and lower vermilion
21		Border of lower vermilion and lower lip
22	Gnathion	Point of maximum curvature of chin
23		External auditory opening

* The facial landmarks are illustrated in Fig. 1.[4]

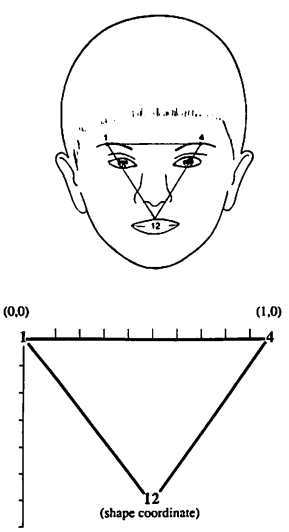


Fig. 2. The triangle formed by the three facial landmarks 1-4-12 is standardized on a cartesian (x, y) coordinate system. Landmark number 12 represents the x, y shape coordinates for this triangle.

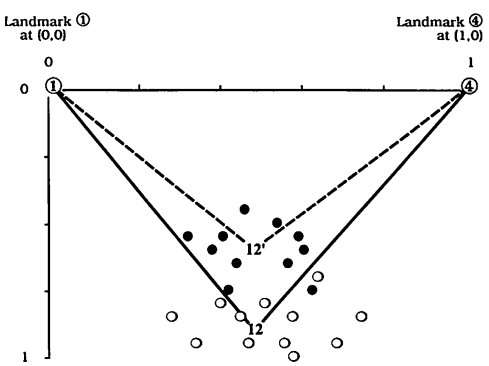


Fig. 3. The shape coordinates (landmark 12) of the exposed (●) and unexposed (O) subjects are displayed as a scatterplot in this hypothetical example. The scatterplot graphically illustrates the position of the midpoint of each child's upper vermilion border (landmark 12) relative to the position of landmarks 1 and 4 on the eyebrows. The *mean* shape coordinates for each group are represented by the average (or centroid) of the scatter of shape coordinates within each group. The locations of the mean shape coordinates for the exposed and unexposed groups are represented by 12′ and 12, respectively. The observed difference in shape between these two mean triangles would be assessed using Hotelling's T^2 statistic.

analysis of landmark data has been described in detail in several publications by Bookstein.[15,16,20] Its application to the study of FAS has also been described.[4,19,21] The use of tensor axes to describe shape change between individual triangles can be extended to describe shape change across the entire set of landmarks using the method of biorthogonal grids.[18,20,22,23] No single triangle of landmarks can be studied independently of the configuration of landmarks around it. Indeed, pictures of tensor axes for triangles can be misleading.[19] Biorthogonal grids (as demonstrated in Fig 8A) depict tensor axes which vary smoothly from place to place over the image. A grid consists of two families of curves which intersect everywhere at 90°. These intersecting curves indicate the directions of greatest (relative) expansion and contraction for a smooth mapping of one landmark configuration into another.

Statistical Analysis

In a previous study,[4] the mean facial shape coordinates associated with triangles 1-4-12, 22-14-19, and 19-23-14 were found to be significantly associated with high levels of prenatal alcohol exposure. These particular triangles were first analyzed to determine whether they differentiated the marijuana- or the alcohol-exposed groups from the unexposed groups in this study. Other triangles, with shapes not so clearly related to FAS, were next evaluated. Because of the exploratory nature of that assessment, formal tests of hypotheses were not emphasized.

The independent and interactive effects of fetal marijuana and alcohol exposure on the x and y coordinate values describing facial shape were assessed by multivariate analysis of variance.[24] Within the context of multivariate analysis of variance, Hotelling's T^2 statistic was used to test explicitly for differences in mean shape between the marijuana- and alcohol-exposed and unexposed groups. To test whether shape changes across all possible triangles, as depicted in the biorthogonal grid, could be described by a simple linear (or homogeneous) model of deformation, another variant of Hotelling's T^2 statistic was used.[19] Under this model, the tensor axes for shape change are the same for all possible triangles.

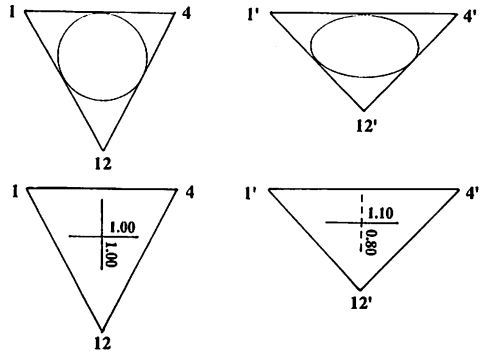


Fig. 4. The transformation of one triangle into another transforms[18] a circle inscribed in the first triangle into an ellipse in the second. The axes (or tensors) of the ellipse, rescaled and oriented homologously in triangle (1-4-12), lie along the directions in which that triangle is most stretched and most compressed by the transformation. The magnitude of the stretching and compression is reflected in the length of the axes. In this hypothetical example, the "deformed" triangle 1'-4'-12' representing the mean shape of the exposed group resulted from a 10% horizontal expansion and a 20% vertical contraction of the "normal" triangle 1-4-12 representing the mean shape of the unexposed group.

Differences in maternal characteristics and infant outcomes between the marijuana- and alcohol-exposed and unexposed groups were evaluated by χ^2 and the t test, where appropriate. Multiple regression analysis was used to evaluate associations between marijuana and alcohol exposure on birth outcome measures and distance measures recorded from the photographs.

RESULTS

Study Population

Of the 61 marijuana-exposed children who were eligible for participation in this study, we were able to locate and enroll 40. These subjects had been last contacted 5 to 7 years previously, when they participated in the original prospective study. Of the 21 mother-child pairs that were not enrolled, 9 could not be located, 2 had moved out of state, 9 were contacted but did not want to participate in the study, and 1 infant had died of sudden infant death syndrome. The mothers of the 40 children who were enrolled in the study differed from the mothers of the 21 children who did not participate in that they were heavier users of marijuana, alcohol, and tobacco and were less likely to have attended college.

From among the 933 eligible nonexposed subjects, the mothers of 70 children were contacted in order to locate and enroll 40 group-matched subjects. Of the 30 subjects who were not enrolled, 24 could not be located, 1 had moved out of state, and 5 expressed no interest in participating in the study. The 40 children with no reported exposure to marijuana were effectively group-matched to the marijuana-exposed group on preconceptional and prenatal alcohol exposure, sex, race, and birth date. Women who reported use of marijuana were, however, more likely to be younger and to be in a lower income bracket and were less likely to be married or to have attended college (Table 2).

Among the 40 marijuana users, 15 reported using marijuana one to two times per week, 11 reported using it three to four times per week, and 14 reported using it every day (Table 3). Fifteen of the women reported smoking marijuana two to five times per day on the days when they used marijuana. The highest reported use of marijuana by one woman was 10 times per day, every day throughout pregnancy to alleviate nausea.

Twelve (15%) of the 80 mothers reported drinking 2 to 4 oz of alcohol per day in the month prior to conception. Ninety-eight percent of the women reported drinking less than ½ oz of alcohol per day during pregnancy. Alcohol consumption prior to and during pregnancy was effectively matched between the marijuana-exposed and unexposed groups (Table 3). Thirteen of the 80 women reported use of cocaine during pregnancy. Cocaine use was more prevalent among the marijuana users.

There were no discernible differences in neonatal status between the marijuana-exposed and unexposed groups (Table 4).

Clinical Assessment of the Photographs

The relationship between maternal use of marijuana in the first trimester of pregnancy and the clinical identification of FAS-like facial characteristics among the children is presented in Table 5. The likelihood of identifying FAS-like facial features among the marijuana-exposed and unexposed groups was essentially the same. Children exposed to marijuana in the first trimester were not more likely to be classified by the dysmorphologist as having FAS-like facial features (as assessed by χ^2). Two children in the marijuana-exposed group were classified as having a probable FAS-like face; the mothers of these children reported consuming 1 or 2 oz of alcohol per day in the month prior to conception. One child in the group unexposed to marijuana was classified as having a probable FAS-like face; the mother had a low AA score in the month prior to pregnancy (0.2 oz/d) but did report two episodes of binge drinking during pregnancy (consumption of five or more drinks per occasion). The lack of association between marijuana and FAS-like facial features was not attributable to differences in sex, race, or age between the two groups. Evaluation of the photographs for facial patterns unrelated to FAS identified a few children with isolated, unusual features but failed to find any consistent patterns that differentiated the marijuana-exposed from the unexposed children.

In contrast, when the 80 children were stratified according to their mother's reported use of alcohol in the month prior to conception, the presence of thin upper lips and somewhat flat philtrums increased in frequency (although not significantly so) with increasing fetal exposure to alcohol (Table 5). It should be noted that maternal use of alcohol in this study population was relatively low compared to the levels of alcohol consumption that have previously been associated with FAS facial features in children. Fetal alcohol syndrome facial alterations have previously been associated with maternal consumption of at least 4 oz of alcohol per day[4,25]; only one child in the current study was exposed to this level of maternal consumption. No child was classified by the dysmor-

TABLE 2. Selected Characteristics of Women Who Did and Did Not Use Marijuana During the First Trimester of Pregnancy*

Characteristic	Marijuana	
	Unexposed (n = 40)	Exposed (n = 40)
Child's race (parent's race)		
White (white)	37	35
White (Oriental)	0	1
White (Chicano)	1	0
White (Native American)	0	1
White (other)	1	0
Black (black)	1	3
Child's age when photographed, y	6.3 (4.9–7.5)	6.3 (5.0–7.4)
Marital status		
Married	37	31
Yearly income†		
<$10 000	1	9
$10 000–$24 999	10	14
>$25 000	27	14
Unknown	2	3
Mother's age at child's birth,‡ y	30.7 (22–48)	26.9 (17–35)
Previous therapeutic abortions‡	0.2 (0–2)	0.7 (0–3)
Previous spontaneous abortions		
1st trimester	0.3 (0–4)	0.2 (0–4)
2nd trimester	0	0.05 (0–2)
Previous stillbirths	0.05 (0–1)	0
No. of pregnancies	2.5 (1–6)	2.6 (1–11)
Mother's education†		
Did not finish high school	0	6
Finished high school only	11	16
Attended college	29	18

* Values represent number or mean (range).
† Significance levels for difference within categories between exposed and unexposed were calculated with χ^2 without Yates' correction: $P < .01$.
‡ Significance levels for difference in means between exposed and unexposed were calculated by t test: $P < .01$.

phologist as having a definite FAS-like face. The proportion of children classified as having a "probable" FAS-like face increased with increasing maternal consumption of alcohol, but the increase was subtle and could have occurred by chance. Marijuana and cocaine use were equally distributed among the women who reported consuming less than 2 oz of alcohol per day prior to pregnancy and the women who reported consuming 2 oz or more per day.

Computerized Morphometric Assessment of the Photographs

In the present study, the shapes of triangles 1-4-12, 22-14-19, and 23-14-19 (previously found to be associated with prenatal alcohol exposure) did not differentiate, to a statistically significant degree, the children exposed to marijuana during the first trimester from the children with no reported exposure to marijuana during gestation. This lack of association persisted even when the exposed group was restricted to those exposed every day. In addition, we were unable to identify any triangles or patterns of minor abnomalies, not previously related to FAS, that differentiated the marijuana-exposed group from the unexposed group. The apparent lack of association between fetal marijuana exposure and facial dysmorphology in this study was not attributable to differences in sex, race, or age between the exposed and unexposed groups.

Shape differences in two of the three triangles previously associated with fetal alcohol exposure[4] were significantly associated with maternal consumption of alcohol in the month prior to conception *among the male children* in this study. It should be noted that in the present study population, alcohol and cocaine exposure was higher among the boys than the girls (Table 6). The sex of the child was also strongly correlated with facial size in this study population. As a result, it was necessary to perform the computerized morphometric assessment separately on the boys and girls. Upon doing so, the mean shape coordinates associated with triangles 22-14-19 and 19-23-14 were found to differentiate boys whose mothers reported consuming ≥ 2 oz of alcohol per day in the month prior to conception (n = 10) from boys exposed to lower levels of alcohol (n = 38) at modest significance levels ($T^2 = 6.65$, $P = .048$ and $T^2 = 6.33$, $P = .054$, respectively) (Fig 5). The tensor axes for this deformation suggested that boys with higher exposure to alcohol had relatively shorter midfaces. This finding was also evident in the measures of midface height recorded directly from the photographs (Table 7). The size of the study population was too small to stratify the alcohol results by marijuana exposure and perform formal tests of significance. Identification of the marijuana-exposed cases on the scatterplot of shape coordinates did, however, confirm that marijuana exposure was not confounding the apparent alcohol effect.

The shape of triangle 23-21-22 also differentiated the boys whose mothers reported consuming 2 to 4 oz of alcohol per day in the month prior to conception

TABLE 3. Other Drug Use Among the Women Who Did and Did Not Use Marijuana During the First Trimester of Pregnancy*

Characteristic	Marijuana	
	Unexposed (n = 40)	Exposed (n = 40)
Trimesters when marijuana was used		
1st only	0	11
1st and 2nd only	0	3
1st and 3rd only	0	2
All three	0	24
Frequency of marijuana use		
1–2 times/wk	0	15
3–4 times/wk	0	11
Every day	0	14
No. of joints smoked per occasion		
1	0	25
2–5	0	14
10	0	1
Trimesters when cocaine was used†		
Never	38	29
1st only	2	7
1st and 2nd only	0	1
1st and 3rd only	0	1
1st, 2nd, and 3rd	0	1
3rd only	0	1
Frequency of cocaine use†		
Never	38	29
<1 time/mo	2	8
1 time/mo	0	1
2–3 times/mo	0	2
No. of times cocaine was used per occasion during pregnancy†		
Never	38	29
1–3	2	9
4–6	0	2
Smoked cigarettes during pregnancy	12	26
No. of cigarettes smoked per day‡		
0	28	14
1–10	6	11
11–20	6	11
21–40	0	4
Average mg of nicotine per day among smokers	6 (0–22)	11 (0–40)
Average oz of alcohol per day in the month before pregnancy (AA score)	0.7 (0–2.0)	0.8 (.01–4.0)
Average oz of alcohol per day during pregnancy (AA score)	0.1 (0–1.0)	0.1 (0–1.0)

* Values represent number of subjects or the mean (range) of the outcome variable.
† Significance levels for differences within the collapsed categories (ever vs never) between exposed and unexposed was calculated using χ^2 without Yates' correction: $P < .01$.
‡ Significance level for difference within categories between exposed and unexposed was calculated using χ^2 without Yates' correction: $P = .009$.

(n = 10) from the boys whose mothers consumed less than 2 oz per day (n = 38) ($T^2 = 10.02$, $P = .01$) (Fig 6). The deformation in the triangle suggested that higher alcohol exposure was associated with retrognathia.

Triangle 22-14-17 (Fig 7) also differentiated the boys whose mothers reported consuming ≥ 2 oz of alcohol per day in the month prior to conception (n = 10) from the boys exposed to less than 2 oz of alcohol per day (n = 38) ($T^2 = 7.92$, $P = .028$). The direction of deformation in this triangle suggested that relative nose lengths were shorter among the boys exposed to higher levels of alcohol. This triangle did not differentiate between the girls with comparable exposures. This finding was corroborated in the distance measures taken directly from the photographs of all 80 children. When nose length, measured directly from the photographs, was regressed on ounces of alcohol consumed per day in the month prior to conception, a significant inverse relationship was noted (Table 7). The sex of the child also influenced nose length, with boys having longer noses than girls. An interaction term between sex and alcohol suggested that the effect of alcohol on nose length differed among the boys and the girls, which is consistent with the results of the digitized analysis of triangle 22-14-17.

Only 2 of the 32 mothers of girls reported consuming 2 oz or more of alcohol per day in the month prior to conception. Although shape changes were not apparent in our analyses of triangles, the sample size was far too small to draw conclusions.

The tensor axes in Figs 5, 6, and 7 appear similarly oriented. A biorthogonal grid was constructed using mean coordinates of lateral landmarks 14 through 23 to summarize the deformational contrasts between the 10 boys whose mothers reported consuming ≥ 2 oz of alcohol/day in the month prior to conception and the 38 boys with less exposure (Fig 8, A). The change in mean shape, as depicted by the biorthogonal grid, describes a shortening of the midface region, especially along the upper midline and retrusion of the chin, relative to the baseline 14-23. The shifts in the 10 mean landmarks between the exposed

TABLE 4. Birth Outcomes Among the Infants Whose Mothers Did and Did Not Use Marijuana During the First Trimester of Pregnancy*

Infant Characteristics	Marijuana	
	Unexposed (n = 40)	Exposed (n = 40)
Child's sex		
Female	15†	17
Gestational age		
<36 wk	0	2
36–42 wk	39	36
>42 wk	1	1
Unknown	0	1
Birth weight		
<2500 g	0	2
2500–4000 g	33	32
>4000 g	7	5
Unknown	0	1
Gestational age, wk	40.0 (36–43)	39.3 (32–43)
Body length, cm	51.1 (46–54)	50.2 (45–56)
Head circumference, cm	34.7 (31–39)	34.2 (31–38)
Apgar score (1 min)		
<7	4	4
7–10	36	35
Unknown	0	1
Apgar score (5 min)		
<7	0	0
7–10	40	39
Unknown	0	1

* Values represent number of subjects or mean (range).
† Group-matched to the exposed group.

and unexposed groups were parallel and for the most part had magnitudes proportional to their mean distances from the baseline (14-23) as would be expected if the overall shape change between groups was linear (or homogeneous) (Fig 8, B).[19] A significant linear shape change across all 10 landmarks was confirmed (F statistic on 2 and 31 *df* = 4.96, *P* = .013). In addition, an F statistic for nonlinearity was computed (F = 1.08 on 14 and 33 *df*, *P* = .40) confirming that the transformation across all triangles was adequately described by a simple (linear) global model. In other words, the directions of expansion and contraction were relatively consistent across all triangles mapped within the boundaries of these 10 landmarks. The linear component of this model explained 50% of the shape change between the two groups.

In the process of evaluating exposure to cocaine as a potential confounder for the facial patterns associated with alcohol exposure, patterns of facial anomalies associated with cocaine exposure were revealed. The mean shape coordinates associated with triangles 23-14-19, 23-14-17, and 23-14-22, all reflecting midface flattening or retrusion, were found to differentiate boys exposed to cocaine during the first trimester (n = 9) from the boys with no exposure to cocaine during pregnancy (n = 38) at modest significance levels (T^2 = 6.44, *P* = .053; T^2 = 8.78, *P* = .019; T^2 = 7.91, *P* =.028, respectively) (Fig 9). Exposure to cocaine on three or more days throughout gestation

TABLE 6. Gestational Exposure to Alcohol and Cocaine Among the Girls and Boys*

Maternal Drug Use	Girls (n = 32)	Boys (n = 48)
Alcohol (oz/d absolute alcohol)		
Month before conception		
0–0.9	18 (56)	24 (50)
1.0–1.9	12 (38)	14 (29)
2.0–4.0	2 (6)	10 (21)
During pregnancy		
0–0.5	32 (100)	46 (96)
1.0	0 (0)	2 (4)
Cocaine (days of use)†		
During pregnancy		
0	29 (91)	38 (79)
1–3	3 (9)	9 (19)
27	0 (0)	1 (2)

* Values represent number of subjects (percent).
† The male-female ratio among the cocaine-exposed group (10 [77%] of 13) is significantly different from an expected 50% (*t* test: *t* = 2.21, *P* = .047).

TABLE 5. Frequency of Fetal Alcohol Syndrome (FAS)-like Facial Characteristics Associated With Maternal Use of Marijuana in the First Trimester of Pregnancy and Alcohol Consumption 1 Month Prior to Conception*

Child's Facial Characteristics	Marijuana		Alcohol†		
	Unexposed (n = 40)	Exposed (n = 40)	0–0.9 (n = 42)	1–1.9 (n = 26)	2–4 (n = 12)
Midface					
Not flat	70	65	67	73	58
Somewhat flat	20	33	28	23	25
Definitely flat	10	2	5	4	17
Philtrum					
Not flat	90	85	93	81	83
Somewhat flat	10	5	7	19	17
Definitely flat	0	0	0	0	0
Upper lip					
Not thin	78	75	81	73	68
Somewhat thin	15	12.5	12	15	16
Definitely thin	7	12.5	7	12	16
Classification of overall facial appearance by dysmorphologist					
No unusual features	85	83	91	80	67
Unusual features, but not FAS-like face	10	10	5	12	25
Possible FAS-like face	2.5	2	2	4	0
Probable FAS-like face	2.5	5	2	4	8
Definite FAS-like face	0	0	0	0	0

* Values represent the proportion of children with the specified facial characteristic.
† AA score: ounces of absolute alcohol per day.

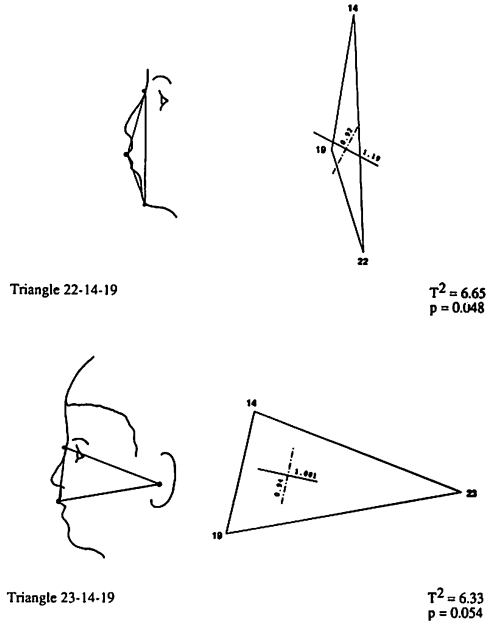


Fig. 5. Two lateral triangles (22-14-19 and 23-14-19) that were found to be associated with prenatal alcohol exposure in a previous study[4] were also found to be associated with fetal alcohol exposure among the boys in the current study. Boys whose mothers reported consuming ≥ 2 oz alcohol/day in the month prior to conception (n = 10) are contrasted with boys whose mothers reported lower alcohol consumption (n = 38).

in 4 boys was associated with increased intercanthal distance relative to palpebral fissure length when compared with the 44 boys with less or no exposure to cocaine ($T^2 = 11.6$, $P = .0065$). Three of these 4 boys received 3 to 9 days of exposure in the first trimester. No associations were observed among the three girls, all of whom were exposed to cocaine only once, in the first trimester. Separate analyses were performed for boys and girls because, as with the alcohol exposure, cocaine exposure was higher among the boys (Table 6) and the sex of the child was strongly associated with facial size. The effects associated with cocaine exposure were not attributable to variation in alcohol, marijuana, or tobacco exposure. The cocaine associations revealed in the landmark analyses were corroborated by the distance measures taken directly from the photographs.

DISCUSSION

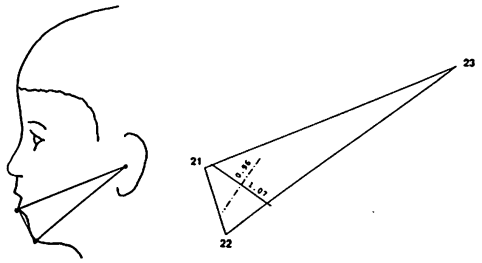
In the current study, fetal marijuana exposure was not found to be associated, to a statistically significant extent, with facial features compatible with FAS. A few epidemiologic and clinical studies, however, have presented evidence suggesting an association between prenatal marijuana exposure and the presence of congenital malformations[26-31] or more specifically, features compatible with FAS.[3,4] The inconclusive nature of these reports can be attributed to one or more of the following factors: weak diagnostic sensitivity, questionable reliability of exposure, inadequate sample size, and/or strongly correlated covariates.

Only one of those studies, to our knowledge, reported a significant association between FAS-like facial features and maternal use of marijuana during pregnancy. In that prospective cohort study of 1690 mother-infant pairs, Hingson et al[2] reported that women who smoked marijuana during pregnancy were five times more likely than nonusers (95% confidence interval = 2.0 to 12; $P = .001$) to deliver a child with FAS-like features. The newborns were examined at 2 to 3 days of age by one of four pediatricians who then completed an anomaly checklist. The authors noted that marijuana use in their study population was strongly correlated with alcohol use. The authors also noted that children of women who averaged two or more drinks daily were not more likely to have FAS-like features when compared with children of women who reported no use of alcohol. Their reported lack of association between FAS-like features and maternal consumption of two to four drinks per day is consistent with other clinical studies. Fetal alcohol syndrome-like features are typically associated with chronic maternal alcoholism.[4] Combining the group that reported consuming two to three drinks per day with the group that reported consuming four or more drinks per day may have weakened the association with FAS-like features. In our digitized analysis of facial form, boys whose mothers reported consuming four or more drinks per day (2 oz or more of alcohol per day) prior to concep-

TABLE 7. Regression of Nose Length and Midface Height Measured Directly From the Photographs of All 80 Children on Sex and Maternal Consumption of Alcohol in the Month Prior to Conception

Variable	b	SE of b	β	F	Sig F
Midface height (entrocanthion to upper lip)*					
AAMB†	−.09	.05	−.18	3.0	.085
Sex‡	−.25	.08	−.36	11.7	.001
(Constant)	5.5	.07		6418.4	.0000
Nose length (entrocanthion to subnasale)§					
AAMB†	−.07	.02	−.43	8.5	.005
Sex‡	−.09	.04	−.41	7.1	.009
Sex × AAMB	.08	.04	.41	5.4	.023
(Constant)	1.69	.03		4131.4	.0000

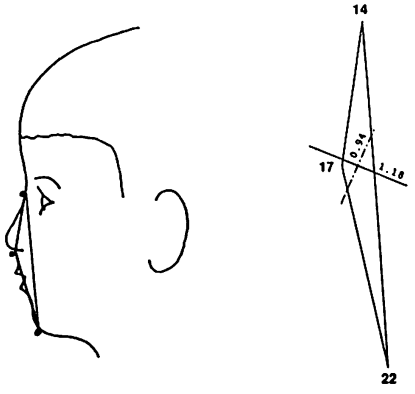
* $r^2 = .15$, F = 6.7, $P = .002$, N = 80.
† AAMB, absolute ounces of alcohol per day in the month prior to conception.
‡ Sex: male = 0, female = 1.
§ $r^2 = .12$, F = 3.4, $P = .022$, N = 80.



Triangle 23-21-22

$T^2 = 10.02$
$p = 0.012$

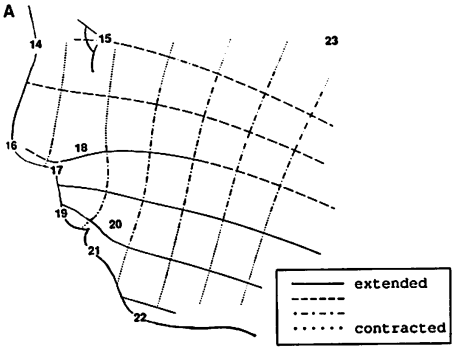
Fig. 6. Retrognathia associated with prenatal alcohol exposure in boys. Boys whose mothers reported consuming ≥ 2 oz alcohol/day in the month prior to conception (n = 10) are contrasted with boys whose mothers reported lower alcohol consumption (n = 38).



Triangle 22-14-17

$T^2 = 7.92$
$p = 0.028$

Fig. 7. Relative decrease in nose length associated with prenatal alcohol exposure in boys. Boys whose mothers reported consuming ≥ 2 oz alcohol/day in the month prior to conception (n = 10) are contrasted with boys whose mothers reported lower alcohol consumption (n = 38).



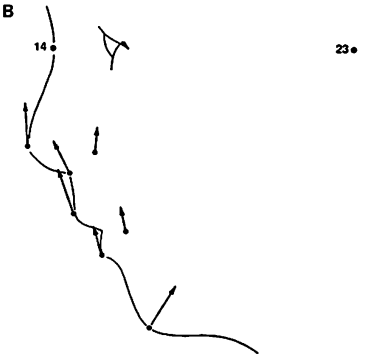


Fig. 8. A, Biorthogonal grid depicting the difference in mean shape between the 10 boys exposed to maternal alcohol consumption of 2 oz or more per day early in pregnancy and the 48 boys exposed to lower levels of maternal alcohol consumption. The grid describes a shortening of the midface region and retrusion of the chin relative to the baseline 14-23. B, Observed shift in the 10 mean lateral landmarks between the exposed and unexposed groups relative to the baseline 23-14.

tion were significantly different from those exposed to lower levels. When the women who reported consuming two drinks per day (1 oz of alcohol) were combined with those who consumed four or more drinks per day, the differences between the two exposure groups (<2 compared with ≥2 drinks) were no longer significant.

In the current study, maternal consumption of as little as 2 oz of alcohol per day, very early in gestation, was associated with FAS-like facial features. Fetal alcohol syndrome-like facial features were not associated with our measures of maternal use of alcohol during pregnancy. Reported use of alcohol during pregnancy was very low in this study population and was comparable in the marijuana-exposed and unexposed groups. Previous studies have suggested that reported use of alcohol in the month prior to conception is a better estimate of the mother's true alcohol consumption during the first 6 to 8 weeks of pregnancy, prior to confirmation of pregnancy. It is during this time period that facial development is most susceptible to teratogens.[32,33]

The deformations depicted by triangles 22-14-19, 22-14-17, 23-14-19, and 23-21-22 and the distance measures recorded directly from the photographs suggested that the children with higher alcohol exposure had shorter noses relative to midface height and were retrognathic. Both of these features are consistent with the FAS facial phenotype. In the current study, the triangular deformations and the distance measures taken directly from the photographs also confirmed that midface length was shorter among the children with higher alcohol exposure. In the literature, the midface is often described as being long relative to the nose. In this study, because all photo-

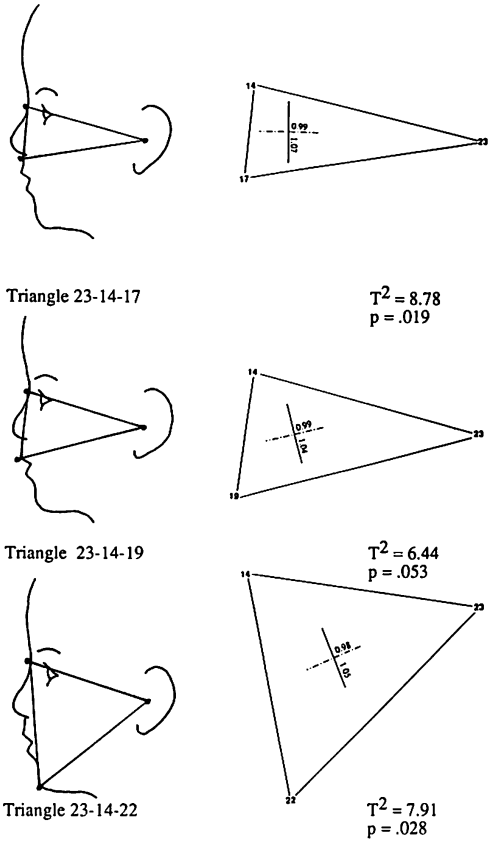


Fig. 9. Midface retrusion associated with first-trimester fetal cocaine exposure among boys. Boys with 1 to 9 days of first-trimester cocaine exposure (n = 9) are contrasted with boys with no cocaine exposure (n = 38).

graphs incorporated a measure of scale, we were able to record real measures of size across all photographs. It appeared that both nose length and midface height decreased with increasing alcohol exposure. In the boys, the mean nose lengths decreased from 3.53 cm to 3.42 cm to 3.25 cm as maternal alcohol consumption increased from (0 to 0.9) to (1 to 1.9) to (2 to 4) oz/d. Correspondingly, mean midface length decreased from 5.51 cm to 5.44 cm to 5.21 cm within each group.

Although triangles 22-14-19 and 23-14-19 were predictive of alcohol exposure in both the current study and the previous study by Clarren and colleagues,[4] it should be noted that the description of shape change for these triangles, as depicted by the directions of the tensor axes, differed. Direct comparisons between the "affected" groups in the two studies cannot be made because of differences in race, sex, and level of alcohol exposure. In the previous study, the group of eight children, among whom significant shape changes were detected, were exposed to 4 oz or more of alcohol per day, were 75% black, and consisted of both boys and girls. A permutation test was used to confirm that there was a significant shape change in these two triangles attributable to ethanol exposure and not to racial differences.

In contrast, in the present study, the group of 10 children among whom significant shape changes were found were exposed to only 2 to 4 oz of alcohol per day and were all boys, and only 10% were black. The shapes of triangles 22-14-19 and 23-14-19 were significantly different between blacks and whites, independent of alcohol exposure. The directions of the tensor axes, attributable to race, roughly match those attributed to alcohol in the previous study. In the current study these two triangles also identify significant contrasts between alcohol-exposed and unexposed groups, independent of race. To determine whether the direction of deformation attributable to alcohol seen in this predominantly white population is the same among a black population, a study sample of exposed and unexposed blacks will need to be assessed.

Two limitations in this study that could have contributed to a false-negative association between marijuana and FAS-like facial features were the reliability of reported drug use and lack of information on use of marijuana in the month prior to conception. Both of these limitations may have resulted in an underestimation of marijuana exposure. In the original prospective study, laboratory drug testing was not performed on all study participants. Instead, validity of self-reported drug use was investigated in a pilot study that preceded the original study. Self-reported drug use was compared to laboratory tests of drug levels present in body fluids in a random sample of 108 postpartum women. The proportion of questionable self-reports ranged from 0% to 3% depending on the drug.[8] These results are encouraging and probably suggest that if drug use has been underreported in this study population, it is unlikely to account for the complete lack of association found between marijuana exposure and FAS-like facial features. Estimating marijuana exposure during the first few weeks of gestation from reports of first trimester use may also have underestimated exposure. Prepregnancy levels of maternal marijuana use may have provided more accurate estimates of fetal exposure in the first 6 to 8 weeks when women are often unaware of their pregnancies. Although actual use of marijuana during the period of facial organogenesis will remain unknown in this study population, a study by Fried and colleagues[34] did find that of three "soft drugs" used by pregnant women (alcohol, nicotine, and marijuana), marijuana use by heavy users was the least reduced between prepregnancy and the first trimester.

To our knowledge, facial alterations associated with fetal cocaine exposure have not been previously reported. The teratogenic potential of cocaine has been documented in both the human[35–37] and animal literature,[38] but contrasting reports do exist.[39–43] Variations in the level and timing of exposure and differences in species susceptibility make it difficult to draw conclusions at this time.

The changes in facial form associated with cocaine exposure in our study population were subtle. Fetal cocaine exposure in this population was associated with increased intercanthal distance and increased midface retrusion. For all practical purposes, these findings would have gone unnoticed. The results should be interpreted cautiously. One cannot infer from the results presented here that fetal cocaine exposure adversely affects craniofacial development. Larger, prospectively designed studies will be required to substantiate these preliminary findings. In light of the prevalence of cocaine use among pregnant women, these preliminary findings strongly support the need for further investigation.

In summary, no dysmorphic facial anomalies were found associated with maternal marijuana use during the first trimester. Several methodologic aspects of this study lend credence to these results. The most sensitive period for the induction of facial malformations lies between the 2nd and 12th weeks of embryonic development.[33] The population we studied received relatively heavy exposure to marijuana during this vulnerable time period. Information on marijuana, alcohol, tobacco, and other drug use during pregnancy was collected prospectively in personal interviews conducted at 1 month postpartum, and the correlation between maternal alcohol and marijuana use during pregnancy was effectively eliminated by group-matching. On the other hand, facial features compatible with FAS were associated with maternal consumption of alcohol in the month prior to conception, substantiating the sensitivity of this diagnostic approach in identifying established syndromal features, even in a relatively small sample.

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Pregnancy Outcomes After Weekly Oral Administration of Ethanol During Gestation in the Pig-Tailed Macaque: Comparing Early Gestational Exposure to Full Gestational Exposure

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ABSTRACT An oral dose of 1.8 g/kg ethanol given once per week throughout gestation to gravid pig-tailed macaques *(Macaca nemestrina)* has been established previously as teratogenic. This study was designed to use this nonhuman primate model to mimic a common problematic human circumstance in which women intermittently abuse alcohol into early pregnancy, realize that they are in fact pregnant, and then want to know the chance that the conceptus is harmed. In order to evaluate this situation, gravid macaques were assigned to one of four dosing cohorts. Animals were given the 1.8 gm/kg dose of ethanol once per week for the first 3, 6, or 24 weeks (full gestation) of pregnancy. Control animals received an isocaloric, isovolemic sucrose solution once per week for 24 weeks. The pregnancies were carefully monitored and the infants were comprehensively evaluated for the first 24 months of life. This paper describes the pregnancies while subsequent papers will describe the infants.

Peak plasma ethanol levels ranged from 175 to 250 mg/dl. Weekly maternal exposure to this intoxicating dose of ethanol, starting early in pregnancy, did not influence risk of pregnancy failure during the first 30 days of gestation but appeared to be associated with an increased risk of abortion occurring between gestational days 30 and 160. Of the pregnancies that were successfully carried to full term, the potentially teratogenic dose of ethanol did not alter pregnancy outcome in any clinically significant way.

INTRODUCTION

Clarren and colleagues reported the development of the first successful binge dosing model for fetal alcohol effects in a nonhuman primate in 1982 (Clarren and Bowden, '82) and then used it to determine the teratogenic threshold for ethanol after once-per-week gestational exposure. The results have been reported in four parts: the methodology and pregnancy outcomes (Clarren et al., '87), the clinical and behavioral assessments of the infants (Clarren et al., '88), a morphometric analysis of the infants' craniofacial shape (Sheller et al., '88) and a neuropathologic and neurochemical assessment of the infants' brains (Clarren et al., '90).

In brief, these studies used gravid female pig-tailed macaques *(Macaca nemestrina)* that were assigned to dosing cohorts and received 0.0, 0.3, 0.6, 1.2, or 1.8 g/kg of ethanol throughout gestation (weeks 1 through 24) or 2.5, 3.3, or 4.1 g/kg of ethanol during weeks 5–24 of gestation (these higher doses were always associated with nonviable pregnancies when given from week 1). The

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infants that resulted from these pregnancies were examined clinically, neurologically and morphologically and assessed by a battery of developmental and cognitive tests. It was determined that exposures which produced mean maternal peak plasma ethanol concentrations (MPPEC) above 140 mg/dl were behaviorally teratogenic and resulted in poor performance on at least part of the psychometric test battery. Behavioral teratogenesis was present in the absence of growth or physical anomalies which corroborate observations in humans that isolated behavioral abnormalities may be a fetal alcohol effect (Streissguth et al., '84). In addition, the infant animals with exposure to mean MPPEC above 140 mg/dl from the first week in gestation were much more severely impaired than animals that were not exposed to ethanol until after the fifth week of gestation, even though the maternal peak plasma ethanol concentrations were much higher (260–540 mg/dl). These results could be seen as "good news" and "bad news" for women who drink during pregnancy. The good news would be that behavioral teratogenesis from weekly drinking, a common drinking pattern among women (Wilsnack et al., '84), was only measurable at levels of ≥140 mg/dl. An average-sized female would have to consume approximately six standard drinks (or 3 ounces of absolute alcohol) to reach a peak plasma ethanol concentration of 140 mg/dl. The bad news would be that the first weeks of pregnancy, a period when many women do not suspect that they are pregnant, may be a period of special vulnerability for ethanol induced fetal brain damage.

The current project was conducted to further assess behavioral and physical teratogenesis associated with early, weekly ethanol exposure, followed by later gestational abstinence. The exposure pattern used in this investigation was designed to mimic a common human situation. That is, women who drink in their usual nonpregnancy pattern find themselves several weeks pregnant and then wonder how much damage may have been done and how much recovery or lack of further damage may occur if alcohol consumption is discontinued. The methodology for this project and the pregnancy outcomes are discussed in this paper. The resultant infant animal development will be presented in subsequent papers.

MATERIALS AND METHODS

Twenty-seven adult female pig-tailed macaques *(Macaca nemestrina)* were selected for this project from the breeding colony of the Regional Primate Research Center at the University of Washington. The criteria for selection were identical to those in the previous study (Clarren et al., '87). The dams had to have a normal physical exam, stable weight, normal complete blood count, normal urinalysis, and normal serum laboratory battery. They were between 5 and 15 years of age with a history of producing at least one viable infant in the previous two years with no unusual history of negative pregnancy outcomes (spontaneous abortions, stillbirths or early neonatal deaths). Eleven equally healthy sires were selected for use in this project from the colony's pool of breeding males.

Timed mating was accomplished by breeding the females at peak tumescence of the vulvar tissues, the period of peak fertility in the animal's menstrual cycle. A laparoscopy procedure was performed within 36 hr of breeding to observe a corpus luteum and confirm ovulation. The laparoscope was inserted through a small incision in the abdominal wall after the animal was anesthetized with intramuscular ketamine of 10 mg/kg. The procedure was generally accomplished in 10–20 min, and the animal was usually fully alert after 1 hr.

When ovulation after copulation was positive, the dam was randomly assigned to one of four dosing cohorts and began its weekly receipt of ethanol or sucrose (control) solution. The ethanol dosage of 1.8 g/kg was selected because of its previously established teratogenic potential. One group of dams received the ethanol dose diluted by volume in four parts of water once-per-week throughout gestation (full gestation equals 24 weeks). A second group received a sucrose solution, isocaloric and isovolemic to the ethanol solution, weekly through gestation. The third group received the ethanol solution for the first three weekly doses and then the sucrose solution through week 24, while the fourth group received the ethanol solution for the first six weekly doses and then the sucrose solution through week 24. The breeding, cohort assignment, and dosing continued until at least seven confirmed pregnancies were followed in each cohort.

Dosing was performed exactly as it was in

the previous study with all animals dosed once a week on the same day of the week (Clarren et al., '87). As animals became available for study, they were dosed on the next scheduled dosing day. This method allowed for exposures across all gestational days. As in the previous study, the animals were maintained in individual cages adjacent to compatible animals in rooms with a general low level of activity helping to minimize stress. They were fed 40 biscuits of Purina Monkey Chow once daily at 3:00 PM and supplemented with apple wedges. Leftover biscuits were counted each morning to monitor food intake. There were no problems with food refusal by the animals. On the day prior to dosing, the animal's food was removed at 5:00 PM in preparation for dosing at 8:00 AM the following morning. The food was removed 15 hours prior to dosing to reduce the variability of plasma ethanol uptake and elimination that results from food consumption (Kalhorn et al., '86). On the morning of dosing, each animal was removed from its cage, without sedation, and weighed. The volume of ethanol or sucrose was calculated and prepared. The resting pulse was recorded. The uterine height was estimated by measuring the external abdominal distance between the top of the symphysis pubis and the palpated uterine fundus. The test solution was then slowly and carefully delivered over a 5-min period through a soft nasogastric catheter (8 Fr.). After dosing, the animal was returned to its cage and observed periodically. Food was reintroduced at 5:00 PM on that day.

Pregnancy was confirmed by uterine palpation 30 days after copulation. Negative palpations at 30 days meant that the female had either not become pregnant or had suffered a direct or indirect embryo toxic event. Animals that were pregnant at 30 days continued to receive a weekly dose of ethanol or sucrose solution until a birth or abortion occurred. When a female was rebred in the project, she was randomly assigned to a different dosing cohort. Females were removed from the breeding pool after a maximum of four negative palpations at 30 days presumed gestation or after two positive pregnancies.

When the dams were within 15 days of their estimated date of delivery, they were watched for signs of labor every 30 min around the clock via a closed-circuit video camera. When labor became active, a study staff member was called to attend the birth. A decision to perform a cesarean section was made if the fetus maintained a consistent breech position after 160 days gestation or if the pregnancy went beyond 180 days gestation without any signs of labor.

Pregnancy outcomes were classified, as in the last study, as follows:

1. *Not pregnant at 30 days gestation.* A corpus luteum was observed by laparoscopy within 36 hr of conception, but a negative palpation was recorded at 30 days gestation. This could represent a failure in conception, a failure in implantation, or an early embryo toxic event.
2. *Abortion.* A spontaneous or therapeutic termination of pregnancy from 30 days confirmed gestation to 160 days gestation.
3. *Stillbirth.* Delivery of a nonviable fetus after 160 days gestation.
4. *Breech birth.* A birth resulting in a nonviable infant due to undetected breech positioning.
5. *Viable infant.* A liveborn infant who survived the perinatal period.

Within 1 month postpartum, the rate of ethanol uptake and elimination in plasma was determined for each dam that gave birth to a viable, full-term infant. A plasma ethanol curve was also generated on the dam that gave birth to a 133-day-old fetus with holoprosencephaly. Determination of plasma ethanol levels were delayed until after birth to minimize handling of the animals during pregnancy. A series of blood samples were collected by recapturing the unsedated animals at 40, 100, 120, 150, and 400 min after administration of a single oral dose of 1.8 g/kg of ethanol. Each 1 ml blood sample was mixed with 1 mg EDTA and chilled on ice. Within 1 hr, the plasma from each sample was transferred to a 0.5-ml microcentrifuge tube and stored at −70°C. Plasma ethanol levels were determined by gas chromatography (Baselt, '87) within 24 hr of acquisition.

RESULTS

Eighty-nine breedings in 27 females and 11 males resulted in 35 pregnancies confirmed by palpation at 30 days gestation. The proportion of negative 30-day palpations ranged from 54% to 65% across the four dose cohorts (Table 1). The variation across the cohorts was not statistically sig-

TABLE 1. Pregnancy confirmation at 30 days gestation among pig-tailed macaques undergoing weekly oral exposure to 1.8 g/kg ethanol or sucrose solution

Duration of weekly maternal exposure (1.8 g/kg EtOH)	No. of dams bred	Not pregnant at 30 days gestation	
		N	%
0 weeks	20	13	65
3 weeks	24	13	54
6 weeks	21	13	62
10 weeks[1]	1	0	0
24 weeks ethanol	23	15	65
Totals:	89[2]	54	61[3]

[1]Originally assigned to the 24-week EtOH cohort. See text for explanation.
[2]There were 89 timed-matings between 27 females and 11 males.
[3]The infant with 10 weeks of ethanol exposure was not included in the total percent calculation.

nificant as assessed by ANOVA. The proportion of animals with negative 30-day palpations observed in this study were similar to the proportions observed in the previous study among the animals exposed weekly to ≤1.8 g/kg. They were also comparable to the overall colony rate of 50% for time-mated pregnancies. Of the 54 matings that resulted in negative 30-day palpations, 47 of the females were tumescing (cycling) within 40 days of ovulation, suggesting that the vast majority of the negative palpations were due to failed conceptions prior to maternal exposure to ethanol. The data extend our conclusions from our previous study that the dose of ethanol which produces behavioral teratogenesis is not an early embryo toxic dose.

Seven of the 35 confirmed pregnancies ended in abortion (Table 2). The abortions occurred in five females, all assigned to ethanol cohorts. The abortions occurred on days 66, 75, 81, 84, 85, 99, and 133 of gestation. The dams were exposed to ethanol weekly through gestational days 31, 25, 23, 43, 21, 45, and 131, respectively. In the previous study one in seven (14%) confirmed control pregnancies ended in an abortion as compared with three of nine (33%) pregnancies exposed weekly to 1.8 g/kg throughout pregnancy. In this study, zero of seven control pregnancies ended in abortion, while seven of 28 (25%) pregnancies exposed to ethanol ended in abortion. Although the rate of abortion was higher in the ethanol cohorts in both studies, the sample sizes were small and the contrasts between the ethanol exposed and unexposed groups in each study were not statistically significant as assessed by χ^2.

One of the seven abortions was a therapeutic abortion. A dam in the 24-week cohort was found to be developing polyhydramnios at 124 days gestation. During the evaluation of this problem, a diagnostic ultrasound at 131 days gestation suggested severe hydrocephalus and possible encephalocele. As a result, a therapeutic cesarean section was performed at 133 days gestation; a female fetus with holoprosencephaly, exencephaly, and an unusual face with median cleft lip and premaxillary agenesis was found. This case has been presented in a separate publication (Siebert et al., '91). The mother of that fetus was exposed to 1.8 g/kg ethanol weekly from day 12 through day 131 of pregnancy with a peak plasma ethanol concentration of 211 mg/dl. One other dam in the study was exposed to ethanol on the same days of pregnancy with a postpartum peak plasma ethanol concentration of 209 mg/dl. A full-term viable female infant was born without complication. The dam that gave birth to the fetus with holoprosencephaly had previously given birth to three viable healthy infants, including one female that was assigned to the control cohort in this study. A different sire was involved in each of her four pregnancies.

Of the remaining 28 gravid females, two more experienced complications during pregnancy. One dam in the 3-week cohort gave birth to a nonviable infant because of undetected breech positioning, and one dam in the 24-week cohort developed an adverse reaction to the alcohol or the intubation procedure characterized by an immediate post intubation production of thick oral pharyngeal secretions. Dosing was discontinued in the tenth week of pregnancy after the second adverse reaction. A viable infant was born to this dam and was evaluated devel-

TABLE 2. Pregnancy outcomes after confirmation of pregnancy in gravid pig-tailed macaques undergoing weekly oral exposure to 1.8 g/kg ethanol or sucrose solution

Duration of weekly maternal exposure (1.8 g/kg EtOH)	Confirmed pregnancies at 30 days	Abortions	Stillbirths	Breech births	Viable births
0 weeks	7	0	0	0	7
3 weeks	11	3	0	1	7
6 weeks	8	3	0	0	5
24 weeks	8	1[1]	0	0	7
Totals:	34	7	0	1	26

[1]Holoprosencephaly and therapeutic abortion.

opmentally but was not entered into any of the ethanol cohort analyses presented in this manuscript, since the dose exposure was unique.

When the 89 mated pairs were divided into three breeding outcome groups (not pregnant at 30 days gestation, abortions or full-term gestations) maternal and paternal age, parity, gestational age at first exposure to ethanol and mean maternal heart rate during the first 30 days of gestation were comparable across the groups (Table 3). Although all seven monkeys that aborted were exposed to ethanol, the proportion of ethanol exposed monkeys in each of the three breeding outcome groups was not significantly different as assessed by χ^2. Dosing was performed once a week on the same day of each week, resulting in seven different gestational exposure patterns, i.e., animals were dosed on gestational days 1, 8, 15, etc., 2, 9, 16, etc., through pattern 7, 14, 21, etc. The earliest exposure to ethanol took place on the third day of gestation; the latest initial exposure took place on the thirteenth day of gestation. The seven exposure patterns were equally represented in each of the four cohorts. Breeding outcomes appeared to be unrelated to the pattern or initial day or week of ethanol exposure in this small group of animals.

In summary, of the 35 confirmed pregnancies, 26 viable infants were born into the four planned cohorts; seven each into the control, 3-week and 24-week exposure cohorts, and five infants into the 6-week exposure cohort. The mean duration of gestation across the four cohorts ranged from 172 to 177 days; the average for the colony is 171 ± 12 days (Table 4). Mean maternal weight gain during pregnancy appeared to decrease with increasing duration of exposure to ethanol (Table 4). Although there were no significant contrasts between cohorts, there was a significant linear trend (one-way ANOVA: $F = 4.9$, $P = .04$). The dams in the control group experienced an average weight gain of 45%, while the dams in the 3-week cohort experienced a 37% weight gain on average and the dams in the 6- and 24-week cohorts achieved a 32% weight gain on average. All of the animals gained weight far better than colony dams as a whole; the average weight gain in pregnancy in the colony is 13% (G.P. Sackett; personal communication). The birthweight centiles for the colony are generated from all births recorded at the Regional Primate Research Center, adjusted for sex, gestational age, and the generation of the dam in the colony. The colony centiles are generated predominantly from infants whose mothers were group-housed in small family units during pregnancy. The dams in this study were placed under more optimal conditions throughout pregnancy, i.e., single-cage housing in a low stress environment with daily monitoring of food consumption. Birthweight centiles would be expected to be higher under these conditions, but not necessarily as high as those observed. The slower weight gain was unrelated to food consumption, maternal age, parity, prepregnancy weight, length of gestation, infant sex, or birthweight.

Among the 26 pregnancies that resulted in viable infants, the mean maternal heart rate throughout pregnancy, across all four cohorts was 148 ± 16 beats per minute (bpm) (Table 4). Maternal heart rates were typically higher during the first few weeks of handling (199 ± 38 bpm) but were comparable across the four cohorts and reduced considerably as the animals became familiar with the dosing procedure. Neither the animals' heart rates nor physical demeanor suggested that the weekly dosing, without sedation, was particularly stressful. For

TABLE 3. Maternal, paternal, and dosing characteristics among the three pregnancy outcome groups

	Not pregnant at 30 days (N = 54)		Abortions (N = 7)		Full-term pregnancies (N = 28)	
Characteristics	Mean	SD	Mean	SD	Mean	SD
Maternal age at the time of mating (yr)	8	1	8	2	8	2
Paternal age at the time of mating (yr)	12	4	11	5	11	3
Parity	3	1	2	1	3	1
Maternal heart rate during dosing in the first 30 days (beats per minute)	194	37	198	29	199	37
Ethanol exposed N (%)	41	76%	7	100%	21	75%
Ethanol exposed in first week N (%)	15	37%	1	14%	9	43%
Gestational age (days) at first ethanol dose N = 41, N = 7, N = 21	9	3	10	2	9	3

TABLE 4. Maternal and infant characteristics within each exposure cohort

	Weeks of gestational ethanol exposure							
	0 (N = 7)		3 (N = 7)		6 (N = 5)		24 (N = 7)	
Characteristics	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Gestation (days)[1]	177	5.0	172	7.0	175	4.0	173	6.0
Maternal weight gain (kg)[2]	2.7	0.6	2.3	0.8	2.0	0.9	2.0	0.3
Percent maternal weight gain	45	14	37	13	32	14	32	8
Parity	2.4	0.5	3.4	1.7	3.0	1.4	2.5	0.9
Birthweight centile[3]	95	4	88	13	91	16	93	9
Female infant N (%)	7	100%	3	43%	3	60%	5	71%
Maternal heart rate during dosing throughout pregnancy (bpm)	145	15	148	11	141	18	155	20
Maternal peak plasma ethanol concentration (mg/dl)	0	0	219	29	231	40	225	25
Caesarean section deliveries, N (%)	2	29%	3	43%	0	0%	1	14%

[1]Includes caesarean section births.
[2]One-way ANOVA, linear trend: F = 4.9, P = .04.
[3]Birthweight centiles are adjusted for sex, gestational age, and the generation of the dam in the colony.

comparison, the mean heart rate of ketamine sedated gravid *Macaca nemestrina* (N = 268), housed under identical conditions with no experimental intervention was 175 ± 30 beats per minute (G.P. Sackett: personal communication).

The plasma ethanol curves demonstrated that the animals achieved peak plasma ethanol concentrations of 175–250 mg/dl, with a mean of 223 ± 28 mg/dl (Table 4). Peaks occurred as anticipated about 120 min after ingestion (Fig. 1). The rates of ethanol uptake and elimination were comparable across all exposed animals and were comparable to the plasma ethanol curves generated from the gravid animals in the previ-

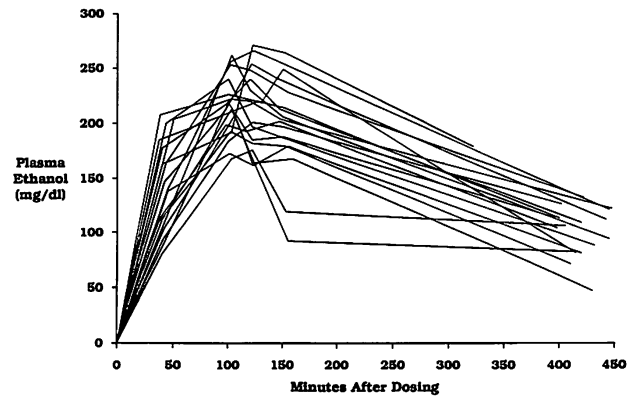

Fig. 1. Plasma ethanol uptake and elimination following a single oral dose of 1.8 g/kg ethanol in each dam that gave birth to a liveborn infant. Plasma ethanol levels were determined within 1 month postpartum.

ous study (Clarren et al., '87) that received 1.8 g/kg ethanol weekly throughout gestation. Most plasma ethanol concentrations remained above 100 mg/dl 400 min after dosing (mean = 104 ± 28 mg/dl across all exposed animals). We chose to monitor plasma ethanol uptake and elimination in the postpartum period to minimize handling of the animals during pregnancy. To confirm that the plasma ethanol curves during the pre- and postpartum periods were comparable, three animals who had plasma ethanol levels measured during pregnancy in the previous study were available during the present study (three years later) for measurement of plasma ethanol levels in the nonpregnant state (Fig. 2). The animals were given a single dose of 1.8 or 2.5 g/kg ethanol to match the dose they received in the previous study. The plasma ethanol levels measured during and after pregnancy overlapped remarkably, suggesting that postpartum measures of plasma ethanol levels may be used as valid estimations of plasma ethanol levels during pregnancy.

DISCUSSION

The primary purpose of this research project was to evaluate ethanol teratogenesis in nonhuman primate infants. The data in this paper are presented to assure the reader that alternate causes for anomaly in these gestations were considered and controlled.

These results confirm and extend our observations from previous work (Clarren et al., '87) that weekly maternal exposure to an intoxicating dose of ethanol (1.8 g/kg), starting early in pregnancy, did not influence the risk of pregnancy failure in the first 30 days of gestation but appeared to be associated with an increased risk of abortion occurring between gestational days 30 and 160. Of the pregnancies that were successfully carried to full term, the potentially teratogenic dose of ethanol did not alter pregnancy outcome in any clinically significant way. There was a statistically significant decrease in the rate of maternal weight gain with increasing duration of exposure, but the mean weight gains in each of the four exposure groups still far exceeded the average maternal weight gain during pregnancy among colony animals. There was no other clinical evidence of maternal ill health or toxicity. No clear explanation for this observation was forth coming.

Theoretically, embryonic exposure to a teratogenic substance in the early implantation period should cause such ubiquitous damage that abortion rather than malformation would be the expected outcome. Following this line of reasoning, some clinicians may have reassured women that if

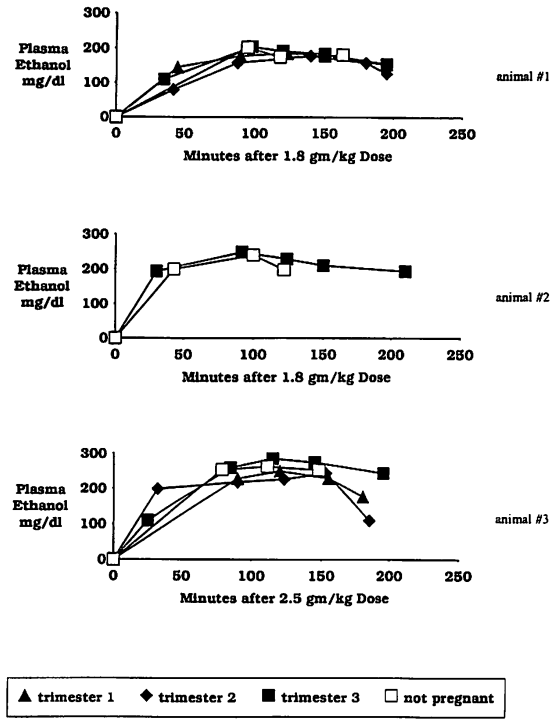

Fig. 2. Plasma ethanol uptake and elimination during and after pregnancy in three pig-tailed macaques *(Macaca nemestrina)* after a single oral dose of 1.8 or 2.5 g/kg ethanol.

they stopped drinking within a few weeks of conception and continued to carry their fetus it was likely that the environmental substance had not produced a teratogenic effect. The data in the present study do not wholly support this type of advice. The apparent increased risk of abortion among these ethanol exposed animals is consistent with the concept of abortion as a teratogenic outcome after early gestational exposure and is consistent with several epidemiologic reports (Harlap and Shiono, '80; Sokol et al., '86; Kline et al., '80). On the other hand, success in carrying a pregnancy to full term does not confirm that the infant has escaped the teratogenic impact of the early gestational exposure. As will be shown in the next paper in this series summarizing infant outcomes, early gestational exposure followed by later gestational abstinence did lead to significant cognitive/behavioral teratogenesis in the offspring.

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Critical Gestational Periods and Threshold Doses for Ethanol Teratogenesis

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Fetal toxicity or teratogenicity involves the passage of substances and/or their metabolites through the gravid female into the developing embryo or fetus. The teratogenic process can be measured by increased fetal wastage and as abnormal outcomes in surviving infants such as overall growth deficiency, major or minor malformations, or central nervous system dysfunction (defined by neurologic, cognitive, or behavioral aberration). These abnormal outcome measures vary in their specificity for the embryo/fetus as compared to the child or adult. Malformation is a unique embryonic response to toxicity. Alterations in growth could occur as a toxic response in the fetal period as well as throughout childhood. Brain dysfunction might occur after toxic exposure at any age. The mechanisms of teratogenesis involve disruption in a series of growth-related activities which are seemingly unique to the prenatal period of life. Organogenesis involves primary cellular differentiations, cellular inductions, cell interactions, secondary cellular differentiations, cell migration, cellular proliferation, and selective cell death.

Teratogenesis might occur through disruption in any or all of these systems globally or in specific embryonic developmental fields. These disruptions might occur through inner cellular mechanisms altering protein synthesis or regulation, or at the level of the cell membranes. Alternatively, disruption could occur through secondary mechanisms like aberrations in placental/fetal blood flow or deranged hormonal balance. The teratogenic potential of a substance to produce anomalies through interference in one or more of these tasks of organogenesis is determined by dosage and mediated through gestational timing of exposure, rates of maternal and fetal metabolism, and possibly by genetic "resistance" of the fetus to the teratogen.

Ethyl alcohol is now well established as a mammalian teratogen. In humans, ethanol can produce all types of teratogenic outcomes: fetal wastage, growth deficiency, major and minor malformations, and neurologic, cognitive, and behavioral dysfunction. One specific ethanol-related teratogenic outcome is fetal alcohol syndrome (FAS), in which growth deficiency for height and weight, brain dysfunction, and a specific set of minor anomalies of the face are combined (Clarren and Smith 1978).

FAS was first described in the early 1970s (Jones et al. 1973). Since then, numerous studies in man and animals have demonstrated that FAS is invariably linked to in utero exposure to ethanol and its metabolites and not to other possible problems in the alcoholic milieu, such as nutritional deficits, smoking, vitamin deficiencies, other substances of abuse, etc. (Schenker et al. 1990). Still, dose-response information for ethanol teratogenesis in human gestation has developed very slowly, and very little is yet known about the precise mechanisms of ethanol teratogenesis.

The study of these basic questions in man has been hampered for numerous reasons. Fetal dose exposure can only be roughly approximated in humans from maternal consumption histories. Even if women can accurately remember the amounts of alcohol consumed during pregnancy, it is essentially impossible to relate this consumption to exact timing in gestation. Further, peak blood alcohol concentrations and rates of ethanol metabolism and excretion will vary and will depend on the rate of consumption, the size (weight) of the mother, the coconsumption of food, the mother's genetic determinants for ethanol metabolism, the existence of liver disease, and day-to-day variations in alcohol metabolism.

Measurement of fetal response to ethanol may be as problematic as accurate measurement of exposure. Determining growth dysfunction or the presence of major malformations is relatively straightforward, but minor malformations may be overlooked or poorly described. It often takes years of careful and extensive sequential testing with appropriate controls before it is clear that an individual has subtle but important aberrations in attention or learning abilities that represent alcohol-related birth defects. The ultimate study of mechanisms of ethanol teratogenesis in humans would require the sequential analysis of affected embryos and fetuses—a situation that is and will remain impossible for all practical purposes.

Over the last decade many small-laboratory-animal models have been developed for ethanol teratogenesis. Models like those developed by West et al. (1990) or Riley (1990) have been used to develop dose-response data and will be used in the future to study the mechanisms of teratogenesis. Yet rodents metabolize ethanol much more rapidly than humans, their gestations are far more rapid, and their brains far less complex. In order to verify that these models are in fact assessing systems that are analogous to humans, a nonhuman primate model can be used.

Methods and Results

We have developed a model for ethanol teratogenesis in the pigtailed macaque *(Macaca nemestrina)* and have used this model to study dose-response principally for brain dysfunction after weekly gestational exposure and the neuroanatomic and neurochemical underpinnings of this dysfunction (Clarren and Bowden 1982).

Our initial studies involved the oral administration of ethanol once per week to gravid pigtailed macaques in doses of 0.3, 0.6, 1.2, 2.5, 3.3, or 4.1 g/kg. A

control group received a sucrose solution which was isocaloric and isovolemic to the highest ethanol dose. Pregnancy was followed after 116 possible timed matings in 54 females.

The pregnancies were carefully monitored such that the control pregnancies and alcohol-exposed pregnancies were similar in all ways except exposure. The day before each dosing session the animals were weighed and the volume of ethanol or sucrose solution was calculated. The animals were denied access to food after 5:00 p.m. in preparation for dosing at 8:00 a.m. the next morning. At dosing, each unsedated animal was brought from its cage and examined. The resting pulse was recorded and the uterine height was measured. The test solution was then slowly delivered via a soft nasogastric tube. The animal was then returned to its cage. Once in every 8 weeks of the 24-week gestation, the dosing procedure was followed by a series of blood samples drawn by femoral venipuncture to determine the curve of ethanol metabolism. In the animals given 0.3 or 0.6 g/kg of ethanol, the animals were recaptured such that blood samples could be obtained 2, 10, 30, 60, and 150 minutes after dosing. In animals given 1.2, 1.8, or 2.5 g/kg of ethanol, blood samples were obtained at 30, 90, 120, 150, and 210 minutes after dosing. In the animals receiving 3.3 or 4.1 g/kg ethanol doses, the blood samples were obtained 30, 90, 120, 150, and 300 minutes after dosing. The samples were spaced so that the peak plasma ethanol concentration (PPEC) could be reasonably established with a reasonable amount of animal handling.

The timing of gestation was established by a laparoscopic finding of a corpus luteum within 36 hours of mating and confirmation of pregnancy by palpation at 30 days gestation. A positive laparoscopic evaluation and subsequent negative 30-day palpation would have indicated a "pregnancy failure" possibly due to a failure in conception, an early embryotoxic event, or an implantation failure. Any spontaneous termination of pregnancy from the time of positive palpation at 30 days to 160 days gestation was called a "spontaneous abortion" in this study while the delivery of a nonviable fetus after 160 days gestation was termed a "stillbirth."

The pregnancy failure rates among animals receiving between 0.3 and 1.8 g/kg of ethanol varied from 36% to 67%. These rates were not statistically different from the study control cases. At the 2.5 g/kg dose and above, no viable infants were produced (Tables 1 and 2). In order to bring some animals to term at these higher dose exposures, a second dose exposure pattern was established in which dosing was delayed until the sixth week in pregnancy and then a dose of 2.5, 3.3, or 4.1 g/kg was given weekly. There was no significant increase in spontaneous abortions from confirmation of pregnancy to term in any group except the group receiving the delayed 4.1 g/kg dose, in which 80% of pregnancies ended in abortion ($p = .008$, binomial test). However, it was noted that among control animals and those with ethanol doses of 1.2 g/kg or less (PPEC $\leq$161 mg/dL), only two of 27 (7%) animals aborted while nine of 21 (43%) animals aborted with PPECs above these levels.

Table 1. Pregnancy failure at 30 days gestation in pigtailed macaques after weekly exposure to ethanol

Dose assignment (g/kg ethanol)	Dams bred (*n*)	30-day pregnancy failures	
		n	%
Delayed dose[a]	23	12	52
Sucrose treated	14	7	50
0.3	21	14	67
0.6	16	9	56
1.2	15	9	60
1.8	14	5	36
2.5	6	5	83
4.1	7	7*	100

[a]No exposure to alcohol or sucrose within the first 30 days of gestation.
*$p = 0.008$ (binomial test).

Table 2. Pregnancy outcome after confirmation of pregnancy in pigtailed macaques undergoing weekly exposure to ethanol

Dose cohorts *(g/kg ethanol)*	Confirmed pregnancies	Spontaneous abortions	Breech stillbirths	Viable infants
Sucrose control	7	1	1	5
0.3	7	—	—	7
0.6	7	1	—	6
1.2	6	—	1	5
1.8	9	3	2	4
2.5	1	1	—	—
2.5[a]	3	1	—	2
3.3[a]	3	—	—	3
4.1[a]	5	4*	—	1
Totals	48	11	4	33

[a] Delayed dose, i.e., no exposure to alcohol in the first 30 days of gestation.
*$p = 0.002$ (binomial test).

Among the female macaques who carried their infants to term, ethanol was well tolerated. Even at the very high 4.1 g/kg exposures, which resulted in PPECs above 500 mg/dL, the animals never became ill or comatose. Rather, the animals would simply sit quietly in their cages after dosing until later on in the day, when they would return to their usual behavior patterns. Aside from the day of dosing, the animals ate normally and gained weight normally through gestation. No serious illness occurred.

When the animals were within 15 days of their estimated full term gestation (172 days), they were transferred to a labor and delivery suite where they were monitored for signs of labor every 30 minutes around the clock by closed-circuit television. When signs of active labor were observed, a member of the delivery team was called to attend the birth.

A total of 33 live-born infant macaques resulted from 48 confirmed pregnancies in 116 matings. Twenty-seven of the animals had been exposed to sucrose or an ethanol solution each week from week 1 to week 24 of pregnancy and were

referred to as FGE (full gestational exposure) animals. Six additional animals had been exposed to the even more substantial ethanol solutions from week 6 to week 24 of pregnancy and were referred to as DGE (delayed gestational exposure) animals.

Each animal was extensively assessed for growth, malformation, and brain function on a battery of tests which extended over the first 6 months of life. Then, at 6 months, each animal was sacrificed so that another battery of neuroanatomic and neurochemical studies could be carried out. While the results of these assessments are summarized here, they are discussed in more detail elsewhere (Clarren et al. 1988, Sheller et al. 1988, Clarren et al. 1990).

The newborn infant exam included ascertaining the Simian Apgar score at 5 and 10 minutes after birth. Additionally, the infants were assessed for rooting, sucking, grasping, eye blinking, and righting reflexes. Birth weight was recorded.

The morning after delivery, a more thorough physical examination of the infant was performed which included measurements of body proportion, pigmentation, head molding, fontanelle size, overriding sutures, facial symmetry, and tooth eruption. Food intake and signs of ill health like sudden fluctuations in weight, diarrhea, or temperaments were noted daily. Each infant had at least one thorough examination for major and minor anomalies by a dysmorphologist.

In addition to regular weights, each animal was measured at regular intervals for foot length, crown rump length, and head length, width, and circumference. Standard frontal and lateral cephalometric radiographs and photographs were obtained at 1 and 6 months of age.

The animals were initially housed in isolettes and weaned to individual cages in a large general infant animal housing suite. Each animal was housed with a parental surrogate (a diaper) until 140 postnatal days of age. There was a daily social experience with a group of like-aged peers in an observation playroom.

Six infant developmental/behavioral measures were employed. Assessments requiring subjective ranking of behavior and/or performance were conducted by testers for whom inter- and intraobserver reliability was high. All testers were blind to the infants' alcohol exposure. The following tests were included:

Neonatal reflex assessments included noting resistance to passive movement of limbs, the strength of grasping, and the presence or absence of the rooting, sucking, and snorting reflexes; observing the infants' auditory startle response, visual orientation and tracking, and the onset of species-specific facial expressions; and testing the leg and arm placing reflex and the clasping and righting reflexes. This assessment was made on the day after birth and twice a week thereafter for 3 weeks.

Nutritive sucking capability was measured from birth to 9 days of age through a device which established the age at which the infant was capable of sucking, the total number of sucks per session, and mean length, amplitude, and velocity of each suck.

The *Object Permanence Assessment* documented the development of object permanence conceptualization from weeks 2–16 based on the procedure devel-

oped by Piaget for human infants (Flavell 1977). The procedure measured the infant's ability to locate and grasp an object (toy) and then, at a later age, the ability to locate the object under conditions of full view, partial hiding, and full hiding behind a screen or in a covered well.

The *Wisconsin General Testing Apparatus* was used to measure early infant learning strategies from 4 to 6 months of age (Harlow 1959). The tests measure an infant's ability to form a systematic pattern of responses while searching for a hidden reward either under or within colored boxes. The tests become more challenging with age.

The *Visual Recognition Memory* test was developed as an early measure of infant intelligence, documenting memory development in the first months of life (Fagan 1977). Visual recognition is measured by recording the proportion of time an infant visually fixates on a familiar object rather than novel two-dimensional abstract patterns. Preferential fixation on a novel pattern demonstrates that an infant can distinguish between two patterns and can remember a pattern previously seen. Human and nonhuman primate infants at risk for intellectual impairment have been shown to direct a lower proportion of their looking time to novel stimuli than do normal infants (Fagan and Singer 1983, Gunderson et al. 1987). Several studies have demonstrated a strong correlation between early visual recognition memory and later cognitive development (Fagan and McGrath 1981, Rose and Wallace 1985).

Playroom motor and behavioral observations were used to further document motor and social development. At 15 days of age the infants were entered into social groups and played daily in a playroom under observation. Motor, postural, and special communication behaviors involving the ability to sit, stand, walk, climb, and display various postures and facial expressions were observed in response to other monkeys and to various apparati in the playroom (Sackett et al. 1976).

Data analysis for each assessment was approached in two ways. First, dose-response relationships between the independent variable (maternal PPEC) and the numerous dependent variables including gestational length, growth parameters (weight, height, head circumference), and the scores for each measure for each of the six developmental tests were analyzed by linear regression. All variables were measured on continuous scales. In addition, comparisons to dose cohort measures for each dependent variable were performed with one-way ANOVA. Since this approach could identify only very robust effects in this small data set, a second approach was employed which identified individual animals with delayed performance for each dependent variable. Delayed individuals were detected by transforming each infant's raw score into a normally standardized Z score. Delayed individuals were defined as those infants with measured scores greater than 2.57 standard deviations (beyond the 99% confidence interval) from the overall mean of the unexposed infants. The tests were scored and the decision made to define an animal as delayed without knowledge of the subject's exposure.

The results of these studies are presented in Figure 1. Each animal is identified

Dose Pattern	Animal I.D.	Cohort	Etoh (g/kg)	MPPEC (mg/dl)	Neurologic Dysmorphic	Microphthalmia Retina gang. loss	Suck response	Obj. perm	WGTA	Visual recog.	Motor dev.	Facial Movm't	Weight	Head Circum.
FULL	1	I	0	0	○○	○○	○○			○	○○		○○	
GEST.	2		0	0	○○	○○	○	○	○	○	○○		○○	
EXPOS.	3		0	0	○○	○○			○	○	○		○○	
	4		0	0	○○	○○	○	○	○	○	○		○○	
	5		0	0	○○	○○	○	○	○	○	○	○	○○	
	6	II	0.3	18	○○	○○		○		○	○		○○	
	7		0.3	23	○○	○○	○○			○	◑	○	○○	
	8		0.3	24	○○	○○	○	○	◑	○	○		○○	
	9		0.3	25	○○	○○	○	○	◑	○	○		○○	
	10		0.3	25	○○	○●	○	○	○	○	○	○	○○	
	11		0.3	25	○○	○○	○						○○	
	12		0.3	26	○○	○○	○	○	○	○	○		○○	
	13	III	0.6	51	○○	●○	○○			○	◑	○	○○	
	14		0.6	51	○○	○○	○	○	○	○		○	○○	
	15		0.6	54	○○	○○	○						○○	
	16		0.6	67	○○	○○	○○		○		○○		○○	
	17		0.6	67	○○	○○	○	○	○	○	○○		○○	
	18		0.6	70	○○	○○	○	○	◑	○	○○		○○	
	19	IV	1.2	115	●○	●○	○	○	○	○	○○		○○	
	20		1.2	117	○○	○○		○		○	○○		○○	
	21		1.2	124	○○	●●	○	○	○	○	○○		○○	
	22		1.2	140	○○	○○	○	●	●	○	○○		○○	
	23		1.2	161	○○	○○	○	○	○	○	○	◑	○○	
	24	V	1.8	189	○○	○●	○	●	◑	○	○○		○○	
	25		1.8	208	◑●	○●	○	●	●	○			○○	
	26		1.8	214	○○	○○	○	○	○	◑	◑	○	○○	
	27		1.8	249	○○	○○	●	○	●	●		○	○○	
DELAYED	28	VI	2.5	260	◑○	○○	○	○	○	○	○○		○○	
GEST.	29		2.5	264	○○	○○	○	○	○	○	○○		○○	
EXPOS.	30		3.3	420	○○	○○	○	○	●	○	◑	○	○○	
	31		3.3	431	○○	○○	○		○	○	●	○	○○	
	32		3.3	432	○○	○○	○	○	○	○	○	○	○○	
	33		4.1	540	◑○	●●		○		○	●	●	●	●

Figure 1. Individual deviations on physical, growth, and developmental parameters are compared in infant macaques exposed to ethanol in utero. Definitions for deviation as denoted by a blackened or half-blackened circle are found in the text. Empty circles indicate normal results, and empty spaces indicate missing or incomplete data (from Clarren et al. 1990).

by individual number, dose cohort, and mean maternal PPEC. While the ethanol exposure in each cohort increased in step increments, variation in maternal metabolism of ethanol produced a continuous array of PPECs. An empty circle on the figure means that a test was completed with normal results, a half-blackened circle means abnormality of approximately 1.5 to 2.5 standard deviations from control means, and a fully blackened circle means deviation beyond 2.5 standard deviations.

Four animals were noted to be neurologically impaired: animals 19, 25, 28, and 33. Animal 19 had four brief grand mal seizures without a metabolic or infectious etiology. The other three animals identified with half-blackened circles in the "neurologic" column had strabismus. Spontaneous seizures are very rare in colony infants and have occurred 0.7% of the time. The chance of one infant in 33 having seizures is 12%. Chernick et al. (1983) described electroencephalogram changes as frequent in human infants exposed to moderate- or high-dose ethanol in utero. Transient infantile strabismus occurs spontaneously in 4% of colony infants. The three affected infants in this study represent 9% of all study infants or 33% of DGE infants and 4% of FGE infants. Strabismus is noted in FAS infants. Further work will be needed before these neurologic abnormalities can be conclusively related to in utero ethanol exposure in this model.

No control animal had any major or minor dysmorphic features. Single minor anomalies were found in three FGE infants and two minor anomalies were found in one DGE infant. This is probably random variation. Only one animal, 25, had a cluster of three minor anomalies typically observed in humans with fetal alcohol syndrome. The anomalies in that animal were carefully evaluated through radiographic morphometric analysis and are described elsewhere (Sheller et al. 1988).

Only animal 33, the lone surviving infant of the DGE 4.1 g/kg dose group (mean maternal PPEC = 539 mg/dL), was growth deficient and microcephalic. The microcephaly was proportionate to body weight. Morphometric analysis performed on cranial radiographs showed that animals exposed to high doses of gestational ethanol had, on average, slightly smaller and distorted crania than control animals (mean two-dimensional cranial area reduced by 1.7% in FGE, 1.8 g/kg animals and DGE animals compared to controls).

No single test of development selected a large group of animals as abnormal, nor were any cohort effects found through analysis of single assessments. However, when the individual animals were assigned individual scores for deviation and plotted on Figure 1, it became clear that the test battery when taken as a whole identified all FGE animals with mean maternal PPEC above 140 mg/dL and three of six DGE animals as abnormal compared to control and lower FGE exposed animals. The scoring of the cognitive/developmental test had been done as follows:

The Object Permanence Assessment was scored using postnatal and postconception age to criterion and number of test sessions to reach criterion. Animals 22, 24, and 25 had consistent delays by all three scoring systems and received full blackened dots.

Four animals, 8, 9, 18, and 24 were delayed significantly on the Wisconsin General Testing Apparatus in completing one or two tasks within this test sequence but were able to complete the full set of nine tasks before 6 months of age. These animals were assigned half-blackened circles. Four other animals, 21, 25, 27, and 30, were so delayed on early Wisconsin tasks that they could not complete the test set by the end of the testing period. These animals were given full blackened circles.

When the Visual Recognition Memory test was scored in the usual manner, no animals were deviant. When the test was assessed as a measure of distractibility, two animals, 26 and 27, stood out as spending excessive time looking away from the targets, varying by more than 2.56 standard deviations from the mean of control animals for time spent looking away. Animal 27 was more deviant than 26.

Animal 27 was also the only animal that did not suck normally by the second day of life, and did not suck until day 5 ($Z = 2.87$).

Finally, among the five measures of motor function observed in the playroom, only six animals were delayed beyond the 99% confidence interval on one or more tasks. Four animals, 7, 13, 26 and 30, failed one or two items and received half-blackened circles, while animals 31 and 33 failed four or five tasks.

The DGE group included the only growth-retarded and microcephalic animal (33) with a mean maternal PPEC of 539 mg/dL. Similar retardation in brain growth had been previously reported in an infant macaque exposed to this same dose and dosing schedule (Clarren and Bowden 1982). Decreased body fat is an important component of the growth deficiency in human children with fetal alcohol syndrome (Streissguth et al. 1984). Normal macaque infants have only 2% body fat at term (Newell-Morris and Fahrenbruch 1985) compared to 15% body fat in term gestation humans (Widdowson 1981), and this may explain why weight deficiency was seen only in very high ethanol exposures in this study.

All animals with mean maternal PPECs above 140 mg/dL in the FGE group were identified as developmentally delayed in some way. Eight of the nine "definitely delayed" scores on the nutritive Sucking Capability test, Object Permanence assessment, Wisconsin General Testing Apparatus, and Visual Recognition Memory assessment occurred in four of these animals. These animals did not demonstrate significant delays in motor and social development as observed in the playroom. Only one of the animals had facial dysmorphia, a finding which strengthens the clinical opinion that human infants gestationally exposed to alcohol may have behavioral teratogenic effects without facial anomalies.

In order to assess the neuroanatomic and neurochemical underpinnings of these cognitive deficits, each animal was sacrificed at 6 months of age. The brain and eyes were removed after sedation with intramuscular Ketamine followed by deep general anesthesia with intravenous chloral hydrate. Each brain was weighed and inspected for gross morphologic abnormalities and then rapidly dissected in a standard fashion for distribution to one of several laboratories. The eyes were transferred for pathology and retina cell counts (Dr. Ann H. Milam's laboratory,

Department of Ophthalmology, University of Washington School of Medicine, Seattle). Cerebral dissection first yielded tissues from the right hemisphere, including samples from the substantia nigra, hypothalamus, frontal gyrus, calcarine cortex, hippocampus and hemibrain stem, the right preoptic area, and the putamen and caudate nuclei. These samples were frozen immediately to be later analyzed for dopamine, DOPAC, norepinephrine, epinephrine, and serotonin (Dr. William J. Shoemaker's laboratory, Neurobiology Laboratory, Department of Psychiatry, University Health Center, Farmington, CT). The left caudate and putamen were dissected in toto from each brain slice, placed on ice, and transferred for immediate assay for dopamine receptors using the ligand-binding technique (Dr. Henry Lai's laboratory, Department of Pharmacology, University of Washington School of Medicine, Seattle).

Samples from the left preoptic area, gyrus rectus, calcarine cortex, right caudate and putamen nuclei, and right cerebellar cortex were placed in Karnovsky's solution for electron microscopic assessment (Dr. P. Kevin Rudeen's laboratory, Departments of Anatomy and Neurobiology, University of Missouri School of Medicine, Columbia). Except for portions of the hippocampal gyrus cerebellum, hypothalamus, and brainstem, which are still under study by Dr. James West (Department of Anatomy, University of Iowa School of Medicine, Ames), the remaining brain tissues were placed in 10% neutral buffered formalin for neuropathologic study (Dr. Clarren's laboratory).

The complete methods for each of these analysis are available elsewhere (Clarren et al. 1990). Data analysis was again approached in two ways. First, formal statistical analyses were carried out to test for associations between ethanol exposure (as measured by maternal PPEC) and each neuroanatomic or neurochemical outcome measure. The chi-square and binomial tests were used. Analysis of variance was used to compare mean outcome scores between exposure cohorts. Multiple regression analysis was used to assess the multivariant influences of maternal PPEC, age and ketamine exposure on the estimation of striatal dopamine, DOPAC and dopamine receptor concentrations. Small sample sizes necessarily limited inferences that could be drawn from these assessments.

In addition to the formal statistical assessments, a more descriptive approach was also employed to identify individual animals that showed evidence of developmental impairment and to identify patterns of effect across all infants as they related to the level and timing of intrauterine ethanol exposure. This approach was helpful in describing the results of the eye pathology. For each animal, the raw score for each outcome measure was transformed into a normally standardized Z score based on the corresponding mean and standard deviation in the unexposed animals. Affected animals were defined as those infants with Z scores > 2.5 standard deviations.

No gross malformations were found in any brain specimen. No abnormalities of cerebral cortices or nuclei, glia, or neurons were confirmed by observation of the brain samples prepared for review with the light microscope.

Tortuosity of retinal blood vessels, a noted feature in humans with FAS, was

not observed in this series of nonhuman primates. Three of the animals, 17, 23, and 33, had bilateral microphthalmia (globe diameter less than 18 mm in all three meridians). Microcornea was observed in the left eye of animal 19. Finally, marked loss of retinal ganglion cells was observed in five of the ethanol-exposed infants, 12, 19, 24, 25, and 33. The pattern of marked ganglion cell loss was always found in only one retina, with mild ganglion cell loss in the opposite retina. Mild ganglion cell loss was found in all of the other ethanol-exposed animals. In the majority (19) of the monkeys, the mild ganglion cell loss was bilateral; in the other two, mild ganglion cell loss was unilateral and the opposite retina had normal ganglion cell counts. The frequency of mild to marked ganglion cell loss in the ethanol-exposed animals (100%) was significantly greater than the frequency of ganglion cell loss in the controls (40%, chi-square = 11.1, $p = 0.0009$ with Yates correction).

Electron micrographic assessments revealed important anatomical differences among cells from animals exposed to different doses of ethanol during gestation. The most striking differences between alcohol-exposed and nonexposed neurons were in the appearance of the endoplasmic reticulum. The cisternae of the endoplasmic reticulum appeared swollen and distended, which resulted in an oval or rounded vacuolar appearance rather than flat membranous stacks. The mitochondria showed a variety of structural changes particularly in the loss of cristae, suggestive of a degenerative condition. This is consistent with mitochondrial abnormalities found in rat pups exposed to a 20% ethanol solution during gestation (Baruah and Kinder 1987). Vesicles were present in the cytoplasm of these cells, and normal-appearing golgi were present with regularly arranged membranous stacks. In some cells, the nucleus appeared related or stellate shaped, whereas this appearance was absent in cells from control animals. The slides from all animals were reviewed without knowledge of exposure and assigned a score for ultrastructural alteration: 1 = normal, 2 = nominally abnormal, 3 = moderately altered appearance, 4 = substantial degeneration in normal appearance of the cell or its organelles, and 5 = maximum abnormal appearance. As seen in Figure 2, the intracellular dysmorphism score appeared elevated among animals, with mean maternal PPECs between 214 and 264 mg/dL in both FGE and DGE groups (animals 26,27, 28, and 29).

Associations were found between mean maternal PPECs, dopamine, and DOPAC concentrations in the striatal nuclei. Ethanol exposure did not appear to influence dopamine concentrations in other brain areas or epinephrine, norepinephrine, or serotonin concentrations. Dopamine concentrations in the striatum varied significantly by animal age and ketamine exposure at the time of sacrifice; however, these factors were accounted for in the analysis (Clarren et al. 1990). Among FGE animals exposed to alcohol, mean maternal PPEC explained 13% of the variance in putamen dopamine concentration [$F(5, 19) = 10.5, p = 0.0001$] and 17% of the variance in the caudate [$F(4, 19) = 6.4, p = 0.0002$]. DOPAC concentrations correlated significantly with dopamine concentrations in the putamen (Pearson correlation coefficient = 0.45, $p = 0.03$). A much weaker correla-

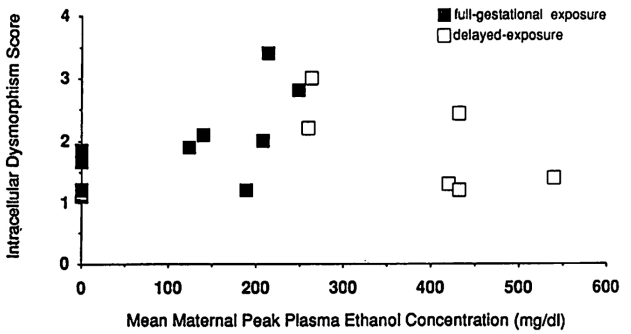

Figure 2. Infant intracellular dysmorphism score as it relates to mean maternal PPEC and timing of ethanol exposure. The intracellular dysmorphism score reflects the extent of intracellular structural alteration observed in the cells of the caudate nucleus. Scores of 1, 2, 3, and 4 reflect normal, minimal, moderate, and substantial alteration in microstructure (from Clarren et al. 1990).

tion between dopamine and DOPAC was found in the caudate (Pearson correlation coefficient = 0.14, $p = 0.14$).

Dopamine receptor levels (fm/mg protein) in the caudate increased gradually with increasing maternal PPEC in FGE animals and increasing age at sacrifice (329–380 days). Maternal PPEC explained 22% of the variance in caudate dopamine receptor levels. In contrast, maternal PPEC had no apparent influence on putamen dopamine receptor levels.

Among the six high-dose animals in the DGE group, putamen and caudate dopamine levels decreased linearly with increasing maternal PPEC. Maternal PPEC explained 95% of the variance in putamen dopamine [$F(1,4) = 83.1, p = 0.0008$] and 68% of the variance in caudate dopamine [$F(1, 4) = 8.7, p = 0.4$].

Putamen and caudate dopamine receptor levels (fm/mg protein) appeared to increase with increasing maternal PPEC among the six delayed-dose animals. Maternal PPEC explained 74% of the variance in putamen dopamine receptor levels [$F(1, 4) = 11.1, p = 0.029$] and 88% of the variance in caudate dopamine receptor levels [$F(2, 3)$ 10.6, $p = 0.04$].

Discussion

This study was undertaken to determine the fetal effects of weekly exposure to ethanol, the most common frequent intermittent consumption pattern among American women (Wilsnack et al. 1984). The goals of the projects were to obtain data that would correlate dose exposure with specific dysfunctional outcomes,

relate phenotypic variables like growth deficiencies and malformation to cognitive and behavioral performance, and relate brain performance to brain structure.

The data suggest that spontaneous abortion is related to weekly ethanol exposures when mean maternal PPEC exceeds 200 mg/dL. In a prospective study of 1200 pregnancies, Sokol et al. (1986) reported an increase in abortions among "heavy drinking" women but did not clarify the specific consumption levels. Kline et al. (1980) reported a case-control study comparing the drinking histories of 626 women who aborted spontaneously with 632 women who carried their pregnancies to at least 28 weeks gestation. Harlap and Shiono (1980) prospectively assessed 32,000 pregnancies and reported a doubling of spontaneous abortions in the second trimester, 14% as compared to 29%, for women drinking one to two standard drinks per day on average. In both of these latter quantitative studies, average alcohol scores were derived by estimating weekly consumption in terms of fluid ounces of absolute alcohol and dividing by seven to obtain an average daily ethanol consumption in ounces per day (Jessor et al. 1968).

The majority of macaques that aborted had mean PPECs above 200 mg/dL. An average-size woman would achieve a comparable PPEC by consuming seven to nine standard drinks containing a total of 2.5 to 4.5 ounces of absolute ethanol (Clarren et al. 1987). Such a weekly amount converts to an average alcohol score of between 0.4 to 0.6, which is comparable to an average alcohol score calculated from the human observations for ethanol exposure and spontaneous abortion by Kline et al. (1980) and by Harlap and Shiono (1980), 0.3 and 0.5, respectively.

Malformations and brain dysfunction became measurable in exposed macaque offspring in early infancy with ethanol exposures at or above 140 mg/dL. This does not mean that weekly dose exposures below 140 mg/dL ethanol were necessarily safe. Marginal developmental delays were identified in the playroom observations and on the Wisconsin General Testing Apparatus in animals in all of the ethanol-exposed cohorts. In addition, further cognitive loss might not emerge until animals become older—at ages beyond the limits of this study. Further, the animals exposed to this dose of alcohol from the first week of gestation were more severe and consistently abnormal than animals exposed to higher doses later on in gestation. This means that exposure to ethanol in humans prior to awareness of pregnancy may be especially harmful. This conclusion is consistent with the findings of Streissguth et al. (1984), who found that cognitive anomalies in children exposed to alcohol in utero were more closely associated with periconceptual maternal drinking than later gestational drinking.

No animal in this study showed all the features of human fetal alcohol syndrome, although every component was seen in some alcohol-exposed animal, with brain problems being the most common.

In the past there has been speculation that "partial" FAS or "possible fetal alcohol effects" might be due to teratogens other than alcohol itself. Our work strengthens the position that these anomalies are related to alcohol teratogenesis directly. It is probable that there is no single dose-response relationship for ethanol

teratogenesis, but rather each abnormal outcome in brain structure or function, morphology, and growth has its own dose-response and gestational timing parameters. FAS should not be seen as the only, most severe, or most important alcohol-related birth defect. It is simply the easiest to recognize.

It is likely that brain dysfunction in our study arose from aberrations in many brain areas. What is important to emphasize here is how subtle the brain findings were at autopsy in spite of clear cognitive deficits in the animals. Up to now only strikingly abnormal brains have been described in the literature as associated with FAS (Clarren et al. 1987). In all probability, most fetal brain damage from alcohol is at the microscopic anatomic or neurochemical level. Computerized tomograms or magnetic resonance images may only rarely image these defects. If *early* gestational exposure to ethanol can lead to obvious behavioral deficits associated with subtle structural damage, it means that ethanol is interfering with brain at a most primitive time in the formation of neural ectoderm. For teratogenesis at that moment to result in only the subtlest of anatomic alteration suggests that the mechanism of damage is in early cellular induction, a time when cells are programmed for later function but their differentiation cannot be detected by current techniques.

Our work helps crystallize human observations with significant implications for epidemiologic studies of the full prevalence of alcohol-related birth defects. Without clinical markers only carefully controlled prospective studies will ever be able to estimate the prevalence of fetal alcohol-induced brain damage. Clinicians will never be able to conclusively prove that isolated brain damage in an individual patient was related to ethanol exposure.

Our studies imply a complex message for public awareness campaigns aimed at preventing alcohol-related birth defects by targeting high-risk populations. On the one hand, measurable brain damage from weekly exposure to alcohol was only consistently found when PPECs exceeded 140 mg/dL. This is the same PPEC West et al. (1990) found related to structural brain teratogenicity for ethanol in rats. The average-size woman would need to consume five to seven drinks each containing 15 cc of absolute ethanol to achieve such a PPEC. This would suggest that real drunkenness could be targeted as a high-risk weekly drinking behavior associated with teratogenesis. On the other hand, damage may be occurring very early in pregnancy prior to the awareness of conception. Since teratogenesis occurs at levels of consumptions far lower than toxic levels, damaged fetuses are likely to be carried to term and their brain damage will only be detected years later. This would imply that if ethanol-related birth defects are to be effectively reduced, warning campaigns could target high-risk drinking behaviors but would need to focus on the *potentially* pregnant women.

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Cognitive and behavioral deficits in nonhuman primates associated with very early embryonic binge exposures to ethanol

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This study was undertaken to evaluate teratogenesis associated with early weekly ethanol exposure followed by later gestational abstinence. Ethanol, 1.8 gm/kg, was orally administered weekly to gravid nonhuman primates *(Macaca nemestrina)* for the first 3, 6, or the entire 24 weeks of pregnancy. Control animals received weekly sucrose solution as did the 3- and 6-week cohort animals in subsequent weeks. Thirty-five viable infants were assessed for growth, malformations, and behavioral and cognitive dysfunction. Animals in the 6-week and 24-week cohorts were uniformly abnormal in behavior and inconsistently abnormal in physical development relative to the control animals. Animals in the 3-week cohort were equivocally normal. These results demonstrate ethanol's capacity to produce behavioral teratogenesis (brain dysfunction) in isolation from physical anomalies in the rest of the body. The results strongly suggest that binge drinking in the first 6 to 8 weeks of pregnancy (a period when women may not know that they are pregnant), followed by later gestational abstinence, is as dangerous to the fetus as exposure throughout gestation. (J PEDIATR 1992; 121:789-96)

A previous study of ethanol teratogenicity in nonhuman primates *(Macaca nemestrina)*[1] demonstrated that (1) cognitive and behavioral abnormalities can occur without accompanying physical anomalies, (2) once-a-week drinking that is not necessarily "alcoholic" can induce fetal brain damage, and (3) early gestational exposure may be more damaging to cognitive function than later and considerably greater ethanol exposure. This last finding is consistent with a report in the human-studies literature that found decreased cognitive function to be more strongly correlated with reported alcohol consumption around the time of conception than with reported alcohol consumption during pregnancy.[2]

ANOVA	Analysis of variance
MPPEC	Mean peak plasma ethanol concentration
WGTA	Wisconsin General Testing Apparatus

This apparent association between early ethanol exposure and cognitive impairment is puzzling because traditional teratologic theory suggests that subtle behavioral deficits not associated with dysmorphic features or obvious structural changes in the brain should be related to late gestational exposure, not early exposure. Moreover, many women are unaware of their pregnancy in the first weeks.

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Table I. Timetable of infant developmental examinations from birth to 2 years of age

Apgar score and physical examination	Birth
Neonatal assessment	Twice a week from birth to 3 wk of age; all examinations performed by a single tester
Visual recognition memory	190, 200, and 210 days of postnatal age
Playroom motor and behavioral development	2 days a week, 10 min/day, from 3 wks to 9 mo of age
Object permanence	3 days a week from 2 wk to 4 mo of age
WGTA memory and learning tasks with measures of activity and distraction	5 days a week from 4 to 14 mo of age
Anthropometric examination and cephalometric x-ray studies	1, 6, 12, and 24 mo of age
Free-play activity levels	1, 6, and 12 mo of age
Growth and health	Monitored continuously

If this period of pregnancy is vulnerable to subtle ethanol-related behavioral teratogenesis and not amenable to repair by subsequent abstinence from ethanol, then prevention strategies need to be directed toward nonpregnant women rather than pregnant women.

We evaluated cognitive, behavioral, and structural teratogenesis associated with early weekly ethanol exposure, followed by later gestational abstinence. We wished to confirm the teratogenicity of weekly exposure to ethanol, 1.8 gm/kg, throughout gestation and to determine whether early gestational exposure to this dose, followed by later gestational abstinence, was as detrimental.

METHODS

Maternal dosing, pregnancy management, and pregnancy outcomes from this project were presented in a separate article.[3] Briefly, one group of pregnant, time-mated pigtailed macaques received a previously established teratogenic dose of ethanol,[1] 1.8 gm/kg, administered orally once a week throughout gestational weeks 1 through 24. The second group of dams received a sucrose solution that was isocaloric and isovolemic to the ethanol solution from weeks 1 through 24. The third group received the ethanol solution in weeks 1, 2, and 3, and then the sucrose solution in weeks 4 through 24. The final group received the ethanol solution in weeks 1 through 6 and then the sucrose solution weekly until the end of pregnancy. There were seven live-born infants in the control group and in the 3-week and 24-week groups, and five live-born infants in the 6-week group. A timetable of the infant examinations is presented in Table I and briefly described below. A more detailed description of infant rearing and examinations was presented previously by Clarren et al.[1]

At birth, 5- and 10-minute Apgar scores were obtained to monitor neonatal well-being. Infant neurologic ratings were also obtained for rooting, sucking, grasping, eye blinking, and righting reflexes. The infants were placed in incubators and cared for 24 hours a day by the infant primate research laboratory nursery staff. A complete physical examination was performed on the day after delivery.

Computerized medical records, including information on pedigree, daily health and clinical care, growth, housing, and hematologic and virologic studies, were maintained on each infant by the full-time veterinary staff. Growth was also followed by obtaining anthropometric measures and standardized frontal and lateral cephalometric radiographs and photographs at 1, 6, 12, and 24 months of age. Anthropometric measures included left foot and crown-rump length, body weight, and head length, width, and circumference. Within the first month of life each infant was scrutinized for major and minor anomalies by a dysmorphologist (S.K.C.).

Infant motor, cognitive, and behavioral development through 14 months of age was evaluated with a battery of developmental assessments: neonatal assessments, object permanence, Wisconsin General Testing Apparatus, visual recognition memory, playroom motor and behavioral development, and free-play activity level in a playroom. The frequency and duration of each examination is presented in Table I. A brief description of each assessment is provided below. All assessments were performed by trained examiners unaware of the exposure history of the infants. Assessments requiring subjective ranking of behavior, performance, or both were conducted by testers for whom interobserver and intraobserver reliability was high. All tests are part of a cognitive-behavioral assessment battery developed and administered at the infant primate research laboratory for more than 20 years. Most were adapted from the human developmental field. The psychometric integrity of the assessment battery has been confirmed in studies conducted during the years.

In general, all infants in the University of Washington Infant Primate Research Laboratory are reared in single cages with surrogate mothers. Although this is not the way monkeys in the wild are reared, "normal" behaviors and development have been established for animals reared in this fashion and can be reliably separated from abnormal behaviors and development.

The neonatal assessment was adapted from the Brazelton

Neonatal Behavioral Assessment Scale.[4,5] Aspects of early functioning that are measured include behavioral state, attention, arousal, and physical responsivity to environmental stimulation. The infants were examined by a single tester who had more than 10 years of experience administering the neonatal assessment. The infants' responses were rated by the examiner on a 3- to 6-point Likert scale (e.g., grasp: 0, none; 1, partial; 2, complete but weak; 3, complete and strong). The full examination required about 15 minutes. Outcomes were scored as the age when a prespecified "mature" response was observed (e.g., mature grasp would be level 3, complete and strong).

The Object Permanence Test Series was adapted from procedures used in human infancy research.[6] Object permanence refers to the extent to which an infant perceives objects as permanent entities (when they are removed from sight) and is considered by many to be the basis for future cognitive operations. As in the human being,[7,8] the onset of this ability is a recognized developmental milestone in the macaque monkey.[9,10] The monkey progresses through the same stages in the acquisition of object permanence as the human being.[11] Both human[12] and macaque infants[11] considered at risk for cognitive impairment lag in the development of object permanence. Outcome is scored as the total number of test days required to reach criterion on each subtest.

The playroom motor and behavioral observations were used to document motor and postural development and the onset of species-typical facial expressions.[13] At 15 days of age the infants were assigned to permanently established social groups that contained five to eight age-matched peers from the colony. The infants in each group were socialized daily in an observation playroom equipped with ramps, shelves, and a few toys. The ages at onset of 12 motor behaviors and 3 facial expressions were recorded during 10-minute observation periods that occurred twice weekly for each infant. Scores were recorded as age at onset of each behavior. Observation continued until all infants in the group reached 9 months of age.

A battery of tests administered with the WGTA provided insight into a range of learning and memory abilities.[14] In general, animals considered at high risk for poor cognitive development perform more poorly than do their normal counterparts on aspects of this battery.[15] Scores for each subtest were recorded in terms of the number of sessions to reach criterion, the number of incorrect responses, or the amount of time required "on task" to figure out the problem.

Throughout the WGTA test battery, behavioral measures were collected. A timer was used to record the time per trial that the infant spent attending and not attending to the stimuli in each of the 13 WGTA tasks. Attention toward the task was defined as eye contact or direct hand contact with the task stimuli. Attention duration provided a measure of how much on-task time an infant required in the performance of the task, whereas the amount of time spent not attending to the task served as a behavioral indicator of distraction. At the end of each test session, the tester rated the infant's overall level of attention and activity during testing on a 5-point ordinal scale. These behavior scores were not collected on the first six infants born into the study but were subsequently adopted.

Infant free-play activity levels were quantitatively assessed at 1, 6, and 12 months of age by recording the animal's activity while alone in an observation playroom that contained shelves at various levels, a ramp, a suspended rope, and two toys. Free-play behavior was recorded for 10 minutes on videotape twice (on 2 separate days within a 1-week period) at each age and coded with single-frame accuracy.[16,17] Infant activity was quantified by measuring the frequency and rate of change of 11 mutually exclusive locomotor and postural behaviors during the 10-minute free-play sessions.

Our test of visual recognition memory is an adaptation of the Fagan Test of Human Infant Intelligence,[11] which indexes attention, discrimination, and memory abilities. Outcome is measured as the proportion of total looking time directed at a novel rather than a familiar stimulus.[12] The development of visual recognition memory in the macaque monkey, as tested by this procedure, has been shown to be similar to that of the human being.[18] Moreover, in both the human being[19] and the macaque monkey,[20] this task has been shown to differentiate between groups of normal infants and those considered to be at risk for cognitive impairment; normal infants usually demonstrate a novelty response, and high-risk subjects either have decreased novelty preference or perform at chance levels.

One-way analysis of variance, the Kruskal-Wallis test, and the chi-square test were used, where appropriate, to detect statistically significant differences between the four ethanol exposure groups. Because of the number of statistical tests that were performed, a more appropriate, albeit conservative, cutoff point for statistical significance would be a p value = 0.002 (Bonferroni adjustment), to reduce the risk of drawing false-positive conclusions. Because of the small sample size (inherent in primate research), only robust differences between exposure groups were statistically detectable. To minimize the risk of drawing false-negative conclusions based solely on statistical evaluations and to capitalize on the broad spectrum of infant outcome measures collected in this study, we placed emphasis on graphically presenting the results of all major outcome variables for each infant relative to the mean performance of the control group. With the exception of the visual rec-

Subject I.D.	Sex	Weeks EtOH	MPPEC mg/dl	Neuro.\Dysm. 1	2	3	Cognitive 4	5	6	Behavior 7	8	9	10	Motor 11	12
1*/IR	F	0	0	○	○	○	○		●					○	○
2*/SU	F	0	0	○	○	○	○	○	●	○	○			○	○
3*/SY	F	0	0	○	○	○	○	○	○	○	○			○	○
4*/VJ	M	0	0	○	○	○	○	○	○	○	○			○	○
5*/GR	M	0	0	○	○	○	●	○	○	○	○			○	○
34/LP	F	0	0	○	○	○	○	○	●			○	○	○	○
35/OH	F	0	0	●	○	○	○	○	○			○	○	○	○
36/SB	F	0	0	○	○	○	○	○	○	○	○	○	○	○	○
37/RS	F	0	0	○	○	○	○	○	○	○	○	○	○	○	○
38/TU	F	0	0	○	○	○	○	○	○	○	○	○	○	○	○
39/VO	F	0	0	○	○	○	○	○	○	○	○	○	○	●	○
40/DX	F	0	0	○	○	○	○	○	○	○	○	○	○	○	○
41/NT	M	3	254	○	○	○	○	○	○			●	●	○	○
42/WC	M	3	240	○	○	○	○	●	○	○	○	○	○	○	○
43/XF	F	3	201	○	○	○	○	○	○	○	○	○	○	●	○
44/AE	M	3	249	○	○	○	○	○	○	●	○	○	○	○	○
45/CF	M	3	176	○	○	○	○	○	●	○	○	○	○	○	○
46/ER	M	3	202	○	○	○	○	●	○	●	○	●	○	●	○
47/UT	F	3	213		○				○						
48/KX	F	6	262	○	○	○	○	●	○			○	●	○	○
49/RG	F	6	179	○	●	○	○	●	●	●	●	●	●	●	○
50/SA	M	6	266	○	○	○	○	○	●	○	●	○	●	●	○
51/SC	M	6	197	○	○	○	○	○	○	○	○	○	●	○	○
52/SR	F	6	253	○	○	○	○	○	●	○	○	●	○	○	●
59/holo	F	18	211		●	●									
53/KJ	M	24	222	○	○	○	●	○	●			○	○	○	●
54/MU	F	24	219	◑	○	○	○	●	●			●	○	●	○
55/SH	M	24	240	○	○	○	○	○	●	●	○	○	○	●	●
56/SI	F	24	208	○	○	○	○	○		○	●	○	○	○	●
57/XZ	F	24	193	○	○	○	●	●	●	○	○	○	○	●	●
58/EY	F	24	220	○	○	○	○	●	●	○	○	●	○	○	●
60/KH	F	24	271	○	○	○	○	●	○	●	○	○	○	●	○
24*/PW	M	24	189	○	○	○	●	○	○	●	○			○	○
25*/XT	F	24	208	◑	●	○	●	●	○	●	○			○	
26*/CD	M	24	214	○	○	○	○	○	○	○	○			○	
27*/AA	M	24	249	○	○	○	○	●	○	●	●			○	○

Figure. Summary of all infant assessments through 6 months of age. Individual deviations on developmental and growth measures are compared in infant macaques exposed weekly to ethanol in utero for 0, 3, 6, or 24 weeks. Extreme deviations from control means are indicated by the symbol ●, while definite but less extreme deviations are indicated by the symbol ◑. Definitions for deviations in each column are found in the Results section. *Absent circles* indicate data not collected. *Asterisks* denote animals from the previous study.[1] The numbers 1 through 12 in the column headings correspond to the following: *1*, neurologic disorders (seizures ●, strabismus ◑); *2*, congenital anomalies (major or fetal alcohol syndrome–like); *3*, microcephaly; *4*, object permanence; *5*, WGTA composite score (memory and learning skills); *6*, visual recognition memory; *7*, distractibility behavior score (ordinal rating during WGTA testing); *8*, activity behavior score (ordinal rating during WGTA testing); *9*, distractibility (time spent off-task during WGTA testing); *10*, activity level (frequency and velocity during free play); *11*, playroom motor development (climbing ramp); *12*, playroom motor development (walking). *ETOH*, Ethanol; *Neuro./Dysm.*, neurologic disorders/dysmorphism; *MPPEC*, maternal mean peak plasma ethanol concentration.

ognition measure, delays were detected in performance or on developmental assessments that were measured on a continuous scale by transforming each infant's raw score into a normally standardized *z* score. Delayed performance was defined as performance resulting in *z* scores ≥ 2 SD from the mean of the control group. This graphic approach was better able to reveal the pattern and extent of developmental impairment in each animal.

Table II. Infant outcomes associated with ethanol exposure

Infant outcome	Gestational ethanol exposure (wk) 0	3	6	24	F*	p	Which groups differ†
Activity							
Mean No. of behaviors/min	12.8 (n = 7)‡	17.8 (n = 6)	30.0 (n = 5)	11.7 (n = 6)	5.2	0.008	6 wk from 0 and 24 wk
Mean frequency of high-energy behaviors§ during 10 min	35.4 (n = 7)	74.5 (n = 6)	130.8 (n = 5)	33.5 (n = 6)	4.4	0.016	6 wk from 0 and 24 wk
Mean activity behavior rating during WGTA testing	2.6 (n = 5)	1.8 (n = 5)	3.4 (n = 4)	2.8 (n = 5)	4.0	0.027	6 wk from 3 wk
Motor development							
Mean age (days) at onset of coordinated walking skill	54.0 (n = 12)	47.8 (n = 6)	58.6 (n = 5)	77.3 (n = 9)	4.6‖	0.041	Linear trend, no two groups differed significantly
Cognitive development							
Mean WGTA composite¶ cognitive score	19 (n = 10)	28 (n = 6)	36 (n = 5)	49 (n = 11)	5.7‖	0.024	Linear trend, no two groups differed significantly
Mean object-permanence composite¶ score	20 (n = 12)	17 (n = 6)	08 (n = 5)	61 (n = 11)	5.2	0.005	24 wk from 0, 3, and 6 wk

*F statistic, one-way ANOVA (‖ weighted linear term).
†Identified by using Student-Newman-Keuls test for multiple comparisons ($p < 0.05$).
‡Sample size variation reflects the inclusion of control animals and 24-week exposure animals from a previous study[1] when data were available.
§High-energy behaviors include swing, run, play, leap, hang, and climb.
¶Higher composite scores reflect poorer performance.

Table III. Mean percentage of looking time to novel stimuli, and mean frequency of fixations and mean duration per fixation to familiar and novel stimuli by ethanol-exposed and unexposed groups

Exposure to 1.8 gm/kg ethanol (wk)	n	Time spent looking at novel stimuli (%)	Frequency of fixations		Duration per fixation (sec)	
			Familiar	Novel	Familiar	Novel
0	12	57.0* ± 7.7	5.0 ± 3.4	4.9 ± 2.6	1.2 ± 0.7	1.4 ± 0.5
3	7	62.6† ± 6.8	4.2 ± 1.3	5.1 ± 1.8	0.8 ± 0.4	1.2 ± 0.7
6	5	52.3 ± 11.4	4.0 ± 1.9	5.1 ± 1.8	1.4 ± 0.6	1.2 ± 0.5
24	10	54.6 ± 12.0	4.9 ± 2.8	4.7 ± 2.4	1.2 ± 0.7	1.4 ± 0.8

Values are mean ± SD.
*Differed from a chance level of 50%, $t(11) = 3.15$, $p < 0.01$ (one-sample t test, two tailed).
†Differed from a chance level of 50%, $t(6) = 4.91$, $p < 0.01$ (one-sample t test, two tailed).

RESULTS

Postnatal growth. All infants had normal weight gain within the first 6 months of life relative to colony-generated norms adjusted for the gender and the number of generations from feral ancestry of each animal. Growth during the first 6 postnatal months in head length, width, and circumference, and in body length and weight, were comparable between the ethanol-exposed and the unexposed animals.

Postnatal health. Postnatal health as measured by the number of treatment days during the first 6 months of life was comparable across all groups of infants. At 39 days of age, one infant in the 3-week cohort (infant 47) had bacterial cultures positive for *Cryptosporidium* and *Campylobacter coli* and died 2 days later. Diarrheal illnesses have been common among colony infants and occurred periodically in every one of the control and ethanol-exposed infants in this study. With the exception of animal 47, all responded favorably to treatment.

The Figure summarizes the results of the infant developmental assessments through 6 months of age as described

in the paragraphs below. The trained examiners in both studies were rotated among all animals to reduce potential tester bias.

Neurologic outcome and congenital anomalies. The frequency of neurologic and congenital anomalies within each exposure cohort are summarized in the Figure. There were no major or minor dysmorphic features among the 12 control animals. One control animal had two brief grand mal seizures at 119 days of postnatal age, a phenomenon that occurs randomly in 1% of colony animals.[1] Of the 24 ethanol-exposed animals, 3 had fetal alcohol syndrome–like facial dysmorphic features. Animal 49 had a flattened, elongated midface. Animal 25 had a flattened philtrum and maxilla, and dental anomalies. One female fetus (animal 59), exposed weekly from gestational age 12 through 131 days, had holoprosencephaly and exencephaly diagnosed at day 133 of gestation. This fetus had the anticipated facial features associated with holoprosencephaly, including premaxillary agenesis and median cleft lip, and has been separately described.[21] No live-born infants had microcephaly or other major malformations of the heart, skeleton, or other organ systems.

Neonatal assessments. The ages when mature responses were attained for the tested motor and behavioral responses (grasp, clasp, self-righting, rooting, snouting, sucking, auditory startle, resistance to passive movement, visual and auditory orientation, visual follow, emotional state, and consolability) were comparable across all exposure cohorts. The mean age to reach the mature response for each behavior ranged from 2 to 4 days in the control subjects. The study had 80% power to detect mean differences as small as 4 days between any two groups at $\alpha = 0.05$ (two sided).

Cognitive development (object permanence and WGTA assessments). One infant in the control group and four infants in the 24-week cohort had significant delay in the 10 object permanence tasks (Figure). The 24-week cohort as a whole required significantly more sessions per task to reach criterion than did the control group and the 3- and 6-week cohorts (ANOVA: $F = 5.2$, $p = 0.005$) (Table II). Infant macaques at risk for cognitive impairment are typically most challenged by the tasks that require them to retrieve objects completely hidden from view.[11] In contrast, the ethanol-exposed infants were most challenged by the tasks that required them to retrieve objects that were in clear view or only partially hidden.

Two infants in the 3-week cohort, two infants in the 6-week cohort, and six infants in the 24-week cohort had significant delay ($\geq$2 SD from the mean composite score of the control cohort) in the memory and learning skills in the WGTA assessment (ANOVA linear trend: $F = 5.7$, $p = 0.02$) (Table II). No one task presented an exceptional challenge to the ethanol-exposed infants. The most striking contrast between the 24-week group and the control group was the time required to accomplish the tasks. The 24-week infants required two or three times more on-task time to discover how to perform the tasks, and on the Hamilton Search measure they had to search through twice as many boxes, compared with the average control infant, to locate the correct box.

Visual recognition memory. The results of the visual recognition memory assessment are presented in Table III. Both the control and 3-week exposure groups had a preference for the novel stimuli, as observed in normal human and macaque infants.[19, 22] In contrast, the 6- and 24-week exposure groups did not demonstrate a preference for either the familiar or novel stimulus.

Behavior during WGTA testing and free play. The ethanol-exposed animals who had higher activity levels, distractibility levels, or both during testing and free-play activity, in comparison with the control group, can be found in columns 7 through 10 in the Figure, and in Table II. The most striking contrast among the exposure groups was the level of activity during the unstructured free-play sessions in the playroom (Figure). The mean frequency and rate of change of free-play locomotor and postural behaviors among the five infants in the 6-week exposure group were twofold to threefold greater than the activity levels observed among the control group and the 3- and 24-week exposure groups (Table II).

Motor development. The onset of locomotor skills such as grasp release, walking, jumping, and climbing were monitored during free-play sessions in an observation playroom. The ethanol-exposed infants, particularly the 24-week exposure group, showed delay in onset ($\geq$2 SD from the mean age at onset for the control group) of two early-acquired skills—coordinated walking and the ability to climb a ramp (Figure; Table II). Additionally, one infant in the 6-week cohort (infant 49) was independently identified by three observers (unaware of the exposure history of the infant) to have a marked lack of motor coordination during the free-play sessions. The infant moved at a rapid pace, often stumbling and falling as a result of what appeared to be poor judgment of her motor capabilities. Her leaps were overambitious and misguided, and she frequently tripped over her own feet when moving across the floor. Although she was delayed at the start in her ability to climb the most easily accessible object, she rapidly attained criteria on the higher-placed shelves, perhaps because of her frequent and unabated attempts to reach them. She was also uncommonly friendly and trusting toward strangers, which is considered maladaptive in this species. She would cling to a stranger with a rough but playful manner and would resist any attempts to be released. This lack of motor coordination and the clinging personality persisted through 3 years of age.

Timing and level of ethanol exposure. We attempted to relate the severity of brain damage to the specific level and

timing of exposure of each animal. Although the mother animals were given the same dose of ethanol for body weight delivered under identical circumstances, their mean peak plasma ethanol levels varied from 176 to 266 mg/dl. Dosing was always initiated on the same day of the week, resulting in seven different dosing schedules relative to the day of conception. No clear patterns were detected relating the initiation, timing, or level of exposure with the type of abnormal outcome observed among animals or the overall severity of impairment observed in each animal. The power to detect patterns, however, was limited because of the few animals that had each dosing pattern. Abortions occurred across all dosing patterns and appeared unrelated to the day of initial exposure.

DISCUSSION

A unique advantage of our functional nonhuman primate model for studying ethanol teratogenesis is its ability to isolate the effects of ethanol from other environmental factors that inevitably plague human research in this area. Our model can be seen as an investigative bridge between studies of small laboratory animals and of human beings. We previously reported that an intoxicating dose of ethanol (achieving maternal mean peak plasma ethanol concentrations >140 mg/dl), delivered only once a week throughout gestation (24 weeks), consistently resulted in behavioral teratogenesis and sporadically resulted in physical teratogenesis.[1] We observed that cognitive abnormalities were more severe and consistent in animals exposed to ethanol during weeks 1 to 24 of gestation whose MPPECs were between 140 and 249 mg/dl than in animals exposed only during weeks 6 to 24 of gestation whose MPPECs were between 260 and 540 mg/dl, thus suggesting an early gestational period for ethanol-induced brain teratogenesis. Additionally, our work confirmed the suspicion in human studies that ethanol-related cognitive and behavioral abnormalities can occur without accompanying physical anomalies and that each affected subject may have a unique cluster of cognitive, behavioral, neurochemical, and/or neuroanatomic aberrations.[1, 23]

These results are important for prevention programs. Ethanol was found to induce fetal brain damage from a common binge pattern of drinking that is not necessarily "alcoholic" and is common in teenagers and young adults[24] who are at higher risk for unplanned pregnancy. The teratogenic threshold occurred at an intoxicating dose of ethanol (1.8 gm ethanol per kilogram of body weight: PPEC >189 mg/dl), which could be achieved by a 55 kg person consuming approximately a six-pack of beer or its equivalent. This teratogenic threshold is similar to one observed in rats.[25]

In our study we confirmed the teratogenicity of this ethanol dose and, in addition, we found that animals exposed to ethanol for only the first 6 weeks of gestation, a period that is roughly equivalent to 7½ weeks in a human being,[26] were indistinguishable, in terms of the frequency of abnormal outcomes identified by the assessment battery, from the animals exposed throughout gestation. The pattern of abnormal outcomes, however, appeared to differ between the two groups. The most striking contrast was the magnitude and consistency of hyperactivity observed among the 6-week exposure cohort during unstructured, free-play activity, a behavioral aberration that was seemingly absent in the 24-week exposure cohort. Hyperactivity and distractibility levels during testing appeared comparable between the two groups, albeit higher than in the control group. The most severely impaired live-born animal received only 6 weeks of ethanol exposure. This animal had significant developmental delay (≥2 SD from the control mean) on seven of the nine assessments and had behavioral and structural anomalies consistent with the diagnosis of fetal alcohol syndrome in human beings.

The frequency of abnormal outcomes in the 3-week exposure group, a period that is roughly equivalent to 3 weeks of gestation in human beings,[26] did not significantly exceed that of the control group, the limited power to detect clinically significant differences (because of the small sample size) precludes the drawing of a conclusion of no effect at this time. However, one animal did show impairment on four separate measures, which suggests the possibility of behavioral teratogenesis even in this gestational period.

It hardly seems appropriate to recommend that women continue to drink alcohol in pregnancy. Unfortunately, the results of our study suggest that weekly exposure to ethanol in the first 6 weeks of gestation is sufficient to produce behavioral and cognitive aberrations, and that the 6-week and 24-week cohorts appear to be at equal risk for damage. There is little evidence in our study that early gestational damage can be repaired by subsequent abstinence, but continued exposure appears to alter the pattern of brain injury. Information currently available suggests that women who stop drinking during gestation have healthier babies—that is to say, larger infants with fewer neonatal problems. We know of no study in human beings that can be compared with the present study.

If our study can be extrapolated to human beings, several implications can be drawn. First, the animals had normal physical examination findings, and most had grossly normal behaviors. Similarly affected human infants therefore would not be identified as abnormal by early physical examination, nor would any single type of early infant assessment have identified many as abnormal. Clinical studies that declare infants normal after in utero ethanol exposure on the basis of an early physical examination or a single developmental test should be considered suspect. Second, mothers who binge-drink, especially in early pregnancy, may not be ad-

dicted to ethanol and may not discuss an alcohol problem with their physicians. It may take rigor on the parts of obstetricians, perinatologists, and others to elicit this important piece of infant-at-risk history. Finally, most studies of human teratogenesis resulting from ethanol exposure report the average alcohol consumption rates during long gestational periods (i.e., first half of pregnancy, second half of pregnancy, or each trimester). The result could be two important methodologic errors. First, the weekly binge dose of ethanol used here would correlate with an average daily exposure of one to one and one-half drinks per day in an average female adult. Recent studies of rats by Bonthius and West[25] suggest that peak exposure, not mean or total exposure, is most important in predicting teratogenic impact. With an average exposure of one to one and one-half drinks per day, some studies have found a teratogenic effect and others have not. These differences might be related to differences in the numbers and types of binge exposures mixed together with lower but more steady exposures. The blending of different exposure periods may dilute early and apparently extremely teratogenic gestational periods.

Extrapolation of these data to other exposure patterns in human pregnancy, for counseling purposes, creates difficult problems. Further controlled studies are needed to establish the consequences of weekly alcohol exposure, twice-a-week exposure, and other exposure patterns. Even without these studies in hand, it is reasonable to assume that many patterns of early gestational exposure to alcohol are likely to cause permanent damage to the offspring.

It would certainly always be wise for women who drink regularly and in large volume to decrease or eliminate alcohol consumption during pregnancy, but our findings do not suggest that abstinence during later pregnancy can prevent or ameliorate early gestational damage from ethanol. The prevention of fetal brain damage from alcohol must rest with the prevention of alcoholism and high-risk alcohol use before pregnancy.

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Immune Function in Offspring of Nonhuman Primates (*Macaca nemestrina*) Exposed Weekly to 1.8 g/kg Ethanol during Pregnancy: Preliminary Observations

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A preliminary investigation of immune host response was conducted in a group of fetal alcohol-exposed nonhuman primates (*Macaca nemestrina*) who were part of a broader ongoing study of ethanol teratogenicity. The mothers of the offspring received weekly oral doses of ethanol (1.8 g/kg) for the first 3 or 6 or the entire 24 weeks of gestation. A control group received sucrose solution weekly throughout pregnancy. Four of the 18 ethanol-exposed animals (22%) died or were euthanized after infectious disease or failure to thrive during the first year of life; none of the seven control animals died. This imbalance in survival prompted the present review of immune function in the remaining offspring. Parameters assessed included: (1) white blood cell count (WBC), (2) peripheral blood leucocyte subsets ($CD4^+$, $CD8^+$, $CD20^+$, and $CD11c^+$), (3) T-cell proliferation after activation with phytohemagglutinin (PHA), staphylococcus enterotoxin B (SEB), and tetanus toxoid (TT), (4) phagocytic activity of monocytes, and (5) serum immunoglobulin levels and serum antibody titers after TT vaccination. Mean T-cell proliferation to TT was significantly decreased ($p = 0.01$) in all ethanol-exposed animals relative to controls, with near-significant decreases ($p = 0.06$) in response to SEB in the ethanol-exposed animals. Lymphocyte proliferation in response to PHA was not altered. Ethanol-exposed animals had significantly lower TT titers than controls after initial vaccination and booster. WBC, leukocyte subsets, serum immunoglobulins, and monocyte phagocytic activity were not significantly different from control values. These preliminary observations suggest that T-cell proliferation and antigen-specific memory responses may be altered in offspring exposed to weekly doses of ethanol in utero and warrant further evaluation for confirmation.

Key Words: Immunity, Prenatal Ethanol Exposure, Immunosuppression, Nonhuman Primate Model, Fetal Alcohol Syndrome.

SINCE THE DESCRIPTION of fetal alcohol syndrome (FAS) in 1973,[1] there has been increasing evidence from human reports and animals studies linking prenatal alcohol exposure and immune deficits.[2] Johnson reported 13 FAS patients with recurrent infections; immunological evaluation showed decreased lymphocyte numbers, decreased in vitro proliferation, and decreased serum immunoglobulins.[3] Steinhausen et al.[4] also reported that FAS children are more susceptible to serious illnesses during their first 2 years of life. Abnormal thymus development and immune deficiency have been associated with in utero alcohol exposure in humans.[5] Since human reports of FAS have imprecise exposure patterns and incomplete medical histories, it is necessary to use animal models with precise ethanol exposures to study the teratogenic effects of ethanol on particular organ systems. Rodent studies have demonstrated that in utero alcohol exposure produces abnormalities in the offspring's developing immune system that persist in adult animals. These have been reviewed by Gottesfeld and Abel[6] and include thymus hypocellularity and proliferation,[7-9] decreased T-cell responses to mitogens,[10,11] inability of T-cells to use interleukin-2,[12] and long-lasting suppression of delayed type hypersensitivity.[13] However, most rodent studies have examined continuous, not binge, alcohol exposure. The advantage of this nonhuman primate study is that it addresses binge ethanol exposure, a common drinking pattern, during variable periods of gestation in an animal model closely related to man.

In the present preliminary investigation, several immunologic and hematologic parameters were evaluated in 17 nonhuman primates (*Macaca nemestrina*) who were part of an ongoing study of ethanol teratogenicity associated with weekly ethanol exposure.[14,15] In the original study, the mothers of 26 offspring received an oral dose of 1.8 g/kg of ethanol weekly for the first 0, 3, 6, or 24 weeks (full gestation) of pregnancy. Precise ethanol exposure information and complete medical histories were available for each animal.

The first indication that ethanol-exposed offspring might be immunocompromised was the 22% mortality due to infectious disease seen in the ethanol exposure groups (two females and two males in the 3- and 24-week ethanol exposure groups) compared to 0% in the control group. We, therefore, investigated whether the surviving ethanol-exposed animals had any alterations in certain hematologic and immunologic parameters. The primary objective of this investigation was to identify associations between fetal ethanol exposure and immune function through exploratory analyses to generate hypotheses for future studies.

METHODS

Animals

In the original study,[14] female pigtailed macaques (*M. nemestrina*) were time-mated at the University of Washington Regional Primate

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Center's breeding facility. Upon confirmation of ovulation, the dams were randomly assigned to one of four exposure groups in blocked fashion to achieve an offspring age balance across the groups. They began weekly receipt of either ethanol (1.8 g/kg) or sucrose solution (isocaloric and isovolemic to the ethanol dose) within the first week of pregnancy. The ethanol and sucrose solutions were administered orally via a soft nasogastric tube.

The four maternal exposure groups included: controls, sucrose solution once per week throughout the 24-week pregnancy; 3-week group, ethanol solution once per week for the first 3 weeks of pregnancy, followed by weekly sucrose solution for the remaining 21 weeks; 6-week group, ethanol solution once per week for the first 6 weeks of gestation, followed by weekly sucrose solution for the remaining 18 weeks; and 24-week group, ethanol solution once per week throughout the 24-week gestation.

The mean maternal peak plasma ethanol concentration was 223 ± 28 mg/dl, a level that could be achieved by a 55-kg person consuming approximately a 6-pack of beer or its equivalent. All offspring were raised under identical environmental conditions.[15]

There were a total of 26 offspring in the original study,[14,15] five of which died or were euthanized before the start of the current immunologic study. We evaluated 21 animals (14 females and 7 males) between 1 and 3 years of age over a 1-year time period: seven animals in the control group, five animals in the 3-week group, five animals in the 6-week group, and four animals in the 24-week group. Four of the 21 animals were viremic for simian D-type retrovirus 2-Washington (SRV-2/Wa; two controls and two 3-week animals) and are not included in this report. All five offspring from control animals were females. There remained one male and two females in the 3-week group, two males and three females in the 6-week group, and one male and three females in the 24-week group. Some of the females were sexually mature. Animals were screened three times for SRV virus, and antibody titers during this 1-year study were all positive for SRV Ab measured by enzyme-linked immunosorbent assay (ELISA) and negative for SRV virus.

Collection of Peripheral Blood and Cell Isolation

After ketamine hydrochloride anesthesia (10 mg/kg), 10 to 15 ml of blood were drawn from the femoral vein into heparinized tubes. Peripheral blood mononuclear cells were obtained by centrifugation of whole heparinized blood over 95% Ficoll-Paque (Pharmacia, Piscataway, NJ) and washed twice in RPMI-1640 and 3% fetal calf serum.[16]

Cell Surface Staining with Monoclonal Antibodies

For measurement of leukocyte subsets, 0.5×10^6 cells were simultaneously stained for 20 min at room temperature with phycoerythrin (PE)-conjugated anti-CD4 [Leu 3a, Becton Dickinson (B-D) Mountain View, CA] and fluorescein isothiocyanate (FITC)-conjugated anti-CD8 (Leu 2a, BD). B-cells were stained with PE-conjugated anti-CD20 (Leu 16, B-D), and macrophages were stained with FITC-conjugated anti-CD11c (Leu M5, B-D). Stained cells were washed, fixed in 1% paraformaldehyde and stored in the dark until analysis within 24 hr. Analysis was performed using an Ortho Cytofluorograph 50 H with model 2150 computer (Ortho Diagnostic Systems, Westwood, MA), as previously described.[17]

Lymphocyte Proliferation

Lymphocyte proliferation was evaluated once or twice after stimulation with phytohemagglutinin (PHA), staphylococcus enterotoxin B (SEB), and tetanus toxoid (TT). For each analysis, blood was obtained from all animals on the morning of the same day. Peripheral blood mononuclear cells were isolated as described above. Cells were cultured in triplicate for 3 days (PHA, SEB) or 6 days (TT) in round-bottom 96-well microtiter plates in 200 μl of growth medium at 1×10^5 cells/well (PHA, SEB) or 2×10^5 cells/well (TT). Lymphocytes were stimulated with PHA (2.5 μg/ml), SEB (100 ng/ml), and TT (25–250 ng/ml). The growth medium was RPMI-1640 supplemented with 10% fetal bovine serum, 100 units/ml of penicillin, 100 μg/ml of streptomycin, and mercaptoethanol (5×10^{-5} M). During the last 12 hr, [^{3}H]thymidine was added at 0.5 μCi/well. Cells were then harvested onto glass fiber filters with a cell harvester and counted in a β-scintillation counter for 1 min, and radioactivity was reported as counts per minute. Lymphocytes incubated with medium alone showed variable and often high background counts; background counts were subtracted from counts per min of stimulated cells. For TT stimulation, the dose resulting in the maximal response was used.

Quantitation of Serum Immunoglobulins (Igs)

Serum immunoglobulin levels (milligrams per liter) were measured once on all animals before tetanus immunization using commercially available radial immunodiffusion assays (Binding Site, Birmingham, United Kingdom). Total serum IgG, IgA and IgM were determined in duplicate, and the mean titer was determined.

Tetanus Immunization and Antibody Titer

The animals were immunized four times (once monthly for 3 months) with 1 ml of TT, given intramuscularly (Lederle, Pearl River, NY), and revaccinated 253 days after the initial vaccination. Tetanus antibody titers (units per milliliter) were determined by ELISA, as previously described,[18] in the laboratory of Dr. David Nelson (National Cancer Institute, Bethesda, MD) before vaccination, 21 and 161 days after the last vaccination, and 28 days after the booster on day 253.

Phagocytic Activity

Phagocytic activity was measured once in all animals. This assay used 24-well plates containing round glass coverslips as adherent surfaces. Mononuclear cells were isolated from blood and seeded into individual wells of slide chambers to ensure surface adherence of 300 to 500 monocytes. Adherent cells in replicate chambers were then exposed to phagocytic particles by the method of Liggitt et al.[19] Two hundred randomly selected cells were counted from each chamber, and the percentages of cells containing zero, one to four, five to seven, or more than eight internalized particles were determined.

SRV Isolation and Detection of Antibody to SRV

All of the offspring were screened for SRV viremia and antibody status three times over the 1-year study. SRV was isolated from lymphocytes by coculturing them with Raji cells.[20] Antibodies to SRV were detected by ELISA[21] using a sodium deoxycholate-disrupted gradient-purified virus antigen.

Statistics

The primary goal of the analysis was to determine if associations could be found between the duration of fetal alcohol exposure and altered immune function in the study group of 17 exposed and unexposed nonhuman primates. Multiple statistical comparisons were conducted in exploratory fashion to generate testable hypotheses for future studies. Performing multiple statistical comparisons increases the probability of identifying false positive associations (type I errors); thus, the p values have been reported for the reader's interest, but should not be strictly interpreted. It should also be noted that because of the small sample size (inherent in primate research), only robust differences between exposure groups were statistically detectable. For the reader's interest, power estimations have been provided, where appropriate, to facilitate interpretation of the negative findings reported in this study.

One-way ANOVA with Scheffes' test for multiple comparisons and the Kruskal-Wallis test were used where appropriate, to evaluate mean

differences among the four exposure groups. The t and Mann-Whitney tests were used, where appropriate, to compare mean differences between the ethanol-exposed group as a whole with the control group.

A balanced ratio of males and females were born to each of the ethanol-exposed groups. The control group, however, was entirely female. The association between gender and exposure was weak and not significant (controls, 100% female; ethanol-exposed, 67% female; $\chi^2 = 0.7$, $p = 0.40$), but the power to detect confounding by gender was too small with the limited sample size; therefore, all analyses were repeated among females only and reported when the results differed from the results of analyses of males and females combined.

RESULTS

Susceptibility to Disease

Four of the 18 ethanol-exposed infants [3-week (one female and one male animal) and 24-week (one female and one male) exposed groups] died or were euthanized due to disease complications or failure to thrive compared with none of seven control animals. Etiologic agents isolated from four animals with diarrhea included *Shigella*, *Cryptosporidia*, and *Campylobacter*.

Lymphocyte Proliferation after Activation with SEB, TT, or PHA

Lymphocyte proliferation differed between the ethanol-exposed animals and the control animals depending upon the T-cell activator used. The mean lymphocyte proliferation in the ethanol-exposed groups after activation with TT was lower (882 ± 1,487 cpm) than that among the control group (2,102 ± 1,500 cpm, Mann-Whitney U = 4.0, $p = 0.01$, Fig. 1B). The contrast was increased when the comparison was restricted to females (mean proliferation to TT = 671 ± 505 cpm), but did not reach statistical significance because of the reduced sample size (Mann-Whitney U = 7.0, $p = 0.09$). Mean lymphocyte proliferation after stimulation with SEB was also lower among the ethanol-exposed groups (13,732 ± 7,011 cpm) relative to the control value (19,147 ± 12,380 cpm), but the difference did not reach statistical significance (Mann-Whitney U = 9.0, $p = 0.06$, Fig. 1A). Mean lymphocyte proliferation after activation with PHA was comparable across all exposure groups (Fig. 1C). The contrasts between exposure groups were not appreciably altered when the analyses for the SEB and PHA experiments were restricted to females. Differences in lymphocyte proliferation were not attributable to differences in the numbers of T-cells placed in culture, since T-lymphocyte fractions were comparable in the ethanol-exposed and unexposed animals (Table 1).

Antibody Titers to TT

Tetanus antibody titers increased after initial vaccination and booster in the control, 6-week, and 24-week exposure groups (Fig. 2). The mean antibody titer was significantly lower in the ethanol-exposed group (2,928 ± 1,357 U/ml) than that in the controls (5,589 ± 2,101 U/ml) after vaccination ($t = 3.1$, $p = 0.007$) and after the booster (ethanol exposed = 37,681 ± 27,110 U/ml versus control = 65,248 ± 11,041 U/ml, $t = 2.2$, $p = 0.04$). The 3-week exposure group showed a consistent and marked lack of antibody response to both the initial vaccination and the booster. The mean tetanus antibody titer after the tetanus booster was significantly lower in the 3-week group (8,635 ± 6,413 U/ml) than in the controls (65,248 ± 11,041 U/ml; one-way ANOVA: $F = 7.0$, $p = 0.005$; Scheffe test: $p < 0.05$). When the ANOVA analyses were restricted to females, the antibody response in the 3-week exposure group was significantly lower after vaccination (979 ± 562 U/ml; one-way ANOVA: $F = 4.0$, $p = 0.05$; Scheffe test: $p < 0.05$) and after booster (5,208 ± 3,434 U/ml; one-way ANOVA: $F = 6.0$, $p = 0.02$; Scheffe test: $p < 0.05$).

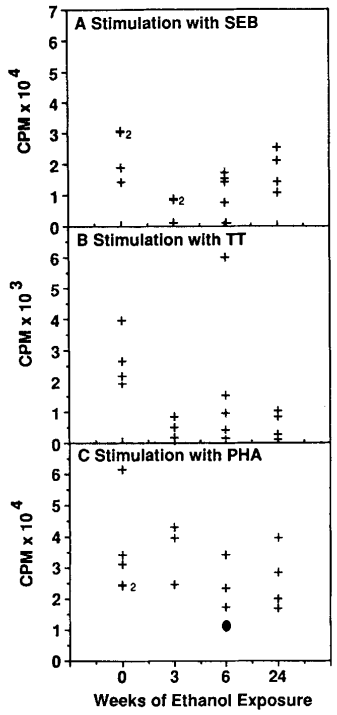

Fig. 1. Peripheral blood lymphocyte proliferation in offspring of *M. nemestrina* exposed to weekly oral doses of 1.8 g/kg of ethanol for the first 3 or 6 or the entire 24 weeks of pregnancy after stimulation with SEB (A), TT (B), and PHA (C) and in controls.

Immunoglobulin Levels

Mean IgG levels were consistently higher in the ethanol-exposed groups than in the controls, but this was not statistically significant (Table 2). The true difference between the mean IgG levels would have had to be greater than 9000 mg/liter for the study to have sufficient power

Table 1. Comparison of Hematocrit, WBC, and Leucocyte Subsets of Offspring of *M. nemestrina* Exposed to Weekly Oral Doses of 1.8 g/kg of Ethanol for the First 3 or 6 or the Entire 24 Weeks of Pregnancy and Controls

Ethanol exposure	n	Hematocrit (%)		WBC × 10^3/ml		T-Lymphocytes %CD4+		T-Lymphocytes %CD8+		B-Lymphocytes % CD20+		Monocytes % CD11c+	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Controls	5	36.1	2.2	9.8	1.7	24.0	3.7	47.4	5.1	10.4	2.6	8.6	1.2
3-week exposed	3	35.5	1.8	10.8	2.9	49.0	6.0	29.0	7.0	7.3	2.9	5.6	3.1
6-week exposed	5	36.3	1.6	10.7	1.4	37.2	6.2	38.0	14.0	6.3	1.3	10.5	9.8
24-week exposed	4	35.3	2.3	10.2	3.7	34.0	14.7	22.7	8.0	13.5	10.1	9.5	5.4

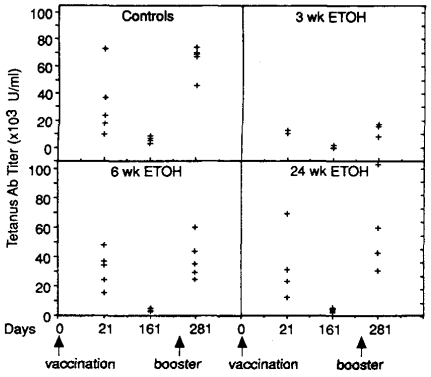

Fig. 2. Tetanus antibody titers (ELISA) in offspring of *M. nemestrina* exposed to weekly oral doses of 1.8 g/kg of ethanol (ETOH) for the first 3 or 6 or the entire 24 weeks of pregnancy and in controls. Tetanus antibody titers were measured before vaccination, 21 and 161 days after vaccination, and 28 days after booster (281 days after the initial vaccination). No animal had an appreciable tetanus titer before vaccination.

Table 2. Immunoglobulin Levels (Milligrams per Liter) in Offspring of *M. nemestrina* Exposed to Weekly Oral Doses of 1.8 g/kg of Ethanol for the First 3 or 6 or the Entire 24 Weeks of Pregnancy and Controls

	Ethanol-exposed			Controls		
	Mean	SD	n	Mean	SD	n
IgG	13,905	4,396	10	11,648	2,971	5
IgA	4,937	2,024	10	4,652	1,460	5
IgM	1,695	602	10	1,580	1,399	4

(80%) to detect it. Mean IgM and IgA levels were also consistently higher in the ethanol-exposed group than in the controls, but the magnitude of difference was not statistically significant. The contrasts between the ethanol-exposed and unexposed groups were not appreciably altered when the analyses were restricted to females.

Hematocrit, White Blood Cell Count (WBC), Leukocyte Subsets, and Monocyte Phagocytic Function

Hematocrits, WBC, and the percentages of T-lymphocytes, B-lymphocytes, and monocytes were comparable in the ethanol-exposed and unexposed animals (Table 1). Monocyte phagocytic function was also comparable in the ethanol-exposed and unexposed groups (data not shown). The above results were not appreciably altered when the analyses were restricted to females.

DISCUSSION

These studies were part of a larger behavioral and neural development study[14,15] and were initiated when the animals were 1–3 years old, after it was noted that there was a 22% mortality in the ethanol-exposed animals (4 of 18) compared to 0% in the control animals (0 of 7). It is important to note that the original study was not designed to evaluate immunologic parameters; the power to draw conclusions from negative associations is very low. It is not the function of this study to draw firm conclusions from these preliminary results, but, rather, to generate hypotheses and report outcome variability, which, in turn, will provide direction and facilitate the design of future studies. It is also important to note that the contrasts observed between the ethanol-exposed and unexposed animals are likely to be underestimated because the study was initiated after the most vulnerable and possibly immunocompromised animals in the ethanol-exposed groups died.

The four animals that died before the initiation of this study succumbed to infectious diarrheal disease. Diarrheal disease is common in laboratory monkeys[22] and *Shigella*, *Campylobacter*, and *Cryptosporidium*[23,24] are isolated in diarrheal episodes in the Infant Primate Laboratory. The majority of animals with infectious diarrheas respond to symptomatic therapy;[22] however, four of the ethanol-exposed offspring developed diarrhea that was refractory to treatment.

The fact that the control group, by chance, was entirely female raised concerns about the potential confounding effect that gender may have on our search for associations between ethanol exposure and immune outcome measures in this study. To address this concern, all analyses were repeated among females only and reported when the results differed from those of analyses of the males and females combined. The only comparisons that differed substantially when restricted to females were lymphocyte

proliferation after activation with TT and antibody response to TT vaccination. In both cases, the difference between the ethanol-exposed and unexposed groups increased. The sample size was too small to infer that males and females respond differently to fetal alcohol exposure. More importantly, these results strongly support the need to control for gender as a potential covariate in the design of future studies.

Although only a small group of animals was available, it is noteworthy that we found significantly decreased lymphocyte proliferation in the ethanol-exposed animals (compared to controls) after stimulation with TT and near-significant abnormalities in T-lymphocyte proliferation after stimulation with SEB. T-cells activated with SEB, a superantigen, showed less proliferation in all of the ethanol-exposed groups, especially in the 3-week exposed animals (Fig. 1A), suggesting abnormalities in T-lymphocytes with T-cell antigen receptor V_β expression.[25,26]

Immunization with tetanus toxoid allowed evaluation of recall responses. This is a sensitive assay of cellular immunity.[27,28] Ethanol-exposed animals had significantly reduced proliferation in response to tetanus antigen compared to that in the control group. The 3-week exposure group was affected the most severely. These findings may be related to abnormalities in antigen presentation, $CD4^+$ T-cell function, or $CD4^+$ help provided to antibody-producing B-cells. Since T-cell responses to lectin activators (such as PHA) are also dependent on adequate antigen presentation, which was not altered in the 3-week exposure group, a defect in antigen presentation is less likely. Decreased T-cell proliferation has been reported in children with FAS[29] and in rodents[8-11] with prenatal ethanol exposure. Antigen-specific memory responses have not been examined in rodent studies with prenatal ethanol exposure.

Children with FAS have decreased percentages of B-lymphocytes in the peripheral blood compared to controls.[29] In this study, 3- and 6-week exposed animals had lower percentages of B-lymphocytes. The magnitude of the decrease between children with FAS and controls was similar to the decrease in 3- and 6-week exposed animals, but these changes were not statistically significant. Nine of 13 children with FAS had decreased serum immunoglobulins.[29] We did not find decreased serum immunoglobulin levels (Table 2).

The mechanisms responsible for altered T-cell function with fetal ethanol exposure will require future studies with particular emphasis on thymic development. Thymic hypocellularity and alterations in thymocyte subsets and proliferation have been associated with in utero alcohol exposure in rodents.[7,8,30,31]

There was considerable variability in the lymphocyte proliferation assay. It is unclear why *M. nemestrina* have such a high variability, but other investigators working with *M. fascicularis*, *P. papio*, and *M. mulatta*[32-34] have also noted a high variability in immune function assays. Since lymphocyte proliferation assays in our laboratory have low variability in inbred pathogen-free mice, the variability is most likely intrinsic to outbred nonhuman primates. Some of the variability may be related to differences in menstrual cycles, which are variable and difficult to detect in young macaques (personal communication, J. Bielitzki).

Most studies evaluating immune function with prenatal ethanol exposure have used rats or mice. This is the first study to evaluate several aspects of host response in a nonhuman primate model, which more closely approximates the placentation and lymphoid system development of man. Our findings are preliminary and need confirmation with further prospectively designed studies.

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Magnetic Resonance Imaging and Spectroscopy in Fetal Ethanol Exposed *Macaca nemestrina*

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ASTLEY, S. J., E. WEINBERGER, D. W. W. SHAW, T. L. RICHARDS AND S. K. CLARREN. *Magnetic resonance imaging and spectroscopy in fetal ethanol exposed Macaca nemestrina.* NEUROTOXICOL TERATOL **17**(5) 523–530, 1995.—Magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (^{1}H-MRS) offer noninvasive ways to observe structural and biochemical changes which might serve as valuable diagnostic markers for detecting brain damage from prenatal ethanol teratogenesis. Cranial MR imaging and spectroscopy were performed on 20 nonhuman primates (*Macaca nemestrina*) with known prenatal ethanol exposures and well-documented cognitive and behavioral levels of performance. The choline : creatine ratio detected by ^{1}H-MRS in the brain increased significantly with increasing duration of in utero ethanol exposure. These signal alterations occurred in the absence of gross structural brain anomalies (detectable by MRI) and were significantly correlated with alcohol-related cognitive and behavioral dysfunction. These observations are consistent with reports of elevated choline : creatine ratios associated with various neurologic insults and disease states. The association observed between brain choline : creatine ratios and in utero ethanol exposure suggest a role for ^{1}H-MRS in elucidating mechanisms of ethanol teratogenicity.

Fetal alcohol syndrome (FAS) Magnetic Resonance Imaging (MRI) Magnetic Resonance Spectroscopy (MRS)
Cholinergic Acetylcholine

A PREVIOUS report has demonstrated that ethanol teratogenicity in nonhuman primates (*Macaca nemestrina*) can result from just once per week binge drinking in only the first 6 to 8 weeks of gestation (5). This exposure can produce cognitive and behavioral abnormalities with or without associated abnormalities in growth or facial form. Magnetic resonance imaging (MRI) and proton spectroscopy (^{1}H-MRS) offer noninvasive ways to observe structural and biochemical changes that might serve as valuable diagnostic markers for detecting brain damage from prenatal ethanol teratogenesis. Cranial MR imaging and spectroscopy were performed on a group of nonhuman primates with known prenatal ethanol exposures and well-documented cognitive and behavioral levels of performance (5,6) to test the usefulness of this technology in this disorder.

METHOD

Study Population, Maternal Dosing, and Infant Developmental Assessment

Cranial MRI and ^{1}H-MRS were performed on the offspring of 20 nonhuman primates (*Macaca nemestrina*) who were prenatally exposed to ethanol or sucrose (control) solution. The mothers of the offspring were time-mated over a period of 1.9 years and randomly assigned to one of four exposure groups. The dams in Group 1 received 1.8 g/kg ethanol once a week for the entire 24 weeks of pregnancy. Group 2 received a sucrose solution that was isocaloric and isovolemic to the ethanol solution once a week for the entire 24 weeks of pregnancy. Group three received the ethanol solution once a week for Weeks 1 through 3 and the sucrose solution

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once a week for Weeks 4 through 24. Group 4 received the ethanol solution once a week for Weeks 1 through 6 and the sucrose solution once a week for Weeks 7 through 24. The ethanol and sucrose solutions were administered orally via a soft nasogastric tube. Dosing was always initiated on the same day of the week, resulting in seven different weekly dosing schedules relative to the day of conception [i.e., gestational days (GDs) 1, 8, 15...; GDs 2, 9, 16...; through GDs 7, 14, 21...]. The distribution of the seven dosing schedules was comparable across the four exposure groups.

MRI and ^{1}H-MRS were conducted in the fall of 1993 when the offspring were between 2.4 and 4.1 years of age (the human equivalent of early to late adolescence). These 20 offspring are the survivors of a larger group of offspring (n = 27) assessed in the original ethanol teratogenicity study (5). They include six offspring in the control group, five in the 3-week ethanol group, five in the 6-week ethanol group, and four in the 24-week ethanol group. A summary of the developmental outcomes, through 6 months of age, for each offspring are presented by animal study number in Fig. 1 in Clarren et al. (5). The offspring included in this MRI/S study include animal numbers 34 through 60, excluding animal numbers 39, 42, 47, 53, 54, 57, and 59. Care and handling of all animals was in accordance with institutional guidelines.

Maternal peak plasma ethanol concentrations were monitored on all dams within 1 week postpartum. The mean peak plasma ethanol concentration among the 14 ethanol exposed animals was 227 ± 33 mg/dl, a level that could be achieved by a 55 kg person consuming approximately 6 to 8 beers or its equivalent. Peak plasma ethanol concentrations were monitored in the postpartum period to minimize handling during pregnancy. Pre- and postpartum plasma ethanol concentrations were confirmed to be comparable (6). Maternal dosing, pregnancy management, and pregnancy outcomes are presented in detail in Clarren & Astley (6).

Infant motor, cognitive, behavioral, and physical development was documented from birth through 24 months of age with a comprehensive battery of assessments which were developed and have been administered at the Infant Primate Research Laboratory for over 20 years (5). Briefly, 5- and 10-min Apgar scores were obtained and a complete physical examination was conducted at birth. Early motor and behavioral reflex responses were monitored from birth through 3 weeks of age using an adaptation of the Brazelton Neonatal Behavioral Assessment Scale (2). Attention, discrimination, and memory abilities were monitored between 2 and 4 weeks of age with an adaptation of the Fagan Test of Human Infant Intelligence (14). Motor and behavioral development during social interaction with age-matched peers in a playroom was recorded twice weekly from three weeks to nine months of age. Object permanence conceptualization, the ability to perceive objects as permanent entities when removed from site, was monitored twice weekly from 3 weeks to 4 months of age using the Object Permanence Test Series. Learning and memory skills were tested daily from 4 to 14 months of age using the Wisconsin General Testing Apparatus (WGTA) (18). Measures of activity and distraction were recorded during all WGTA test sessions. Free-play activity level in an observation playroom was recorded and coded on videotape at 1, 6, and 12 months of age. Infant growth and craniofacial development was documented through anthropometric examination and collection of standardized cephalometric X-rays and photographs at 1, 6, 12, and 24 months of age. Detailed descriptions of infant rearing, assessment, and developmental outcomes through the first 6 months of life can be found in Clarren et al. (5,7).

In this MRI/S study, an unweighted composite score reflecting each animal's developmental impairment through 6 months of age was derived by dividing the number of assessments an animal failed by the number of assessments used to summarize each animals' development in Fig. 1 presented in Clarren et al. (5). Failure for each assessment was defined as

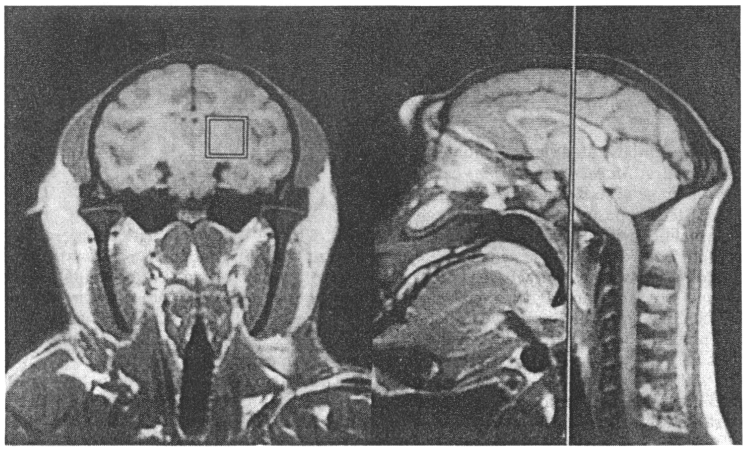

FIG. 1. Coronal and sagittal T1-weighted magnetic resonance images (400–550/12, repetition/echo times in ms), defining the region of interest for magnetic resonance spectroscopy. The center of the 3.4 cc volume of interest was selected on a coronal image selected from a sagittal localizer to include thalamus, parts of the internal capsule and basal ganglia, and adjacent white matter.

(a) performance > 2 SDs below the mean performance of the control animals or (b) presence of a neurologic disorder/congenital anomaly.

MRI and ^{1}H-MRS

MRI and ^{1}H-MRS were carried out on a General Electric Signa whole body MR Scanner operating at 1.5 Telsa, using version 4.6 software and hardware. The animals were sedated with an intramuscular injection of ketamine/xylazine (10 mg/kg), placed in prone position, and aligned comparably (Frankfort Horizontal plane at 90°; to the horizontal axis of the scanner) in a knee coil with the aid of a custom designed stereotaxic head holder. A knee coil was used to accommodate the small size of the animals' heads. Although blood gas or oximetry data was not collected, respiration was visually monitored and postioning in the Frankfort Horizontal alignment facilited maintanence of a free airway. MRI and ^{1}H-MRS were obtained sequentially utilizing the same hardware. The entire procedure (alignment, imaging, and spectroscopy) required approximately 60 min of sedation time.

The MRI study was performed first and included T1-weighted sequences in the sagittal and coronal planes, and both T1 and T2-weighted images in the axial plane. Sequence parameters for T1-weighted images were repetition time (TR) 400–550 ms and echo time (TE) 12 ms. Parameters for T2-weighted images were TR 2500 ms and TE 23 and 80 ms. A 16-cm field of view was utilized with slice thickness of 3 or 4 mm.

MR coronal images were used to define a 3.4 cc brain region of interest for spectroscopy (Fig. 1). Volume-localized spectra were achieved using the point resolved spectroscopy (PRESS) pulse sequence (27). This pulse sequence uses 90°–180°–180° radio frequency pulses and has three water suppression radio frequency pulses with gradient spoilers. Magnetic field homogeneity was adjusted with the *X*, *Y*, and *Z* gradients using the localized voxel immediately before spectral data acquisition. The acquisition parameters were: TR 2000 ms; TE 136 ms; voxel size 3.4 cc; sweep width of 1000 Hz; spectral frequency 63.8 MHz; number of acquisition points 1024; number of averages 100.

The above parameters result in acquisition of spectra with three principle resonances: choline-containing compounds (Cho), creatine-containing compounds (Cr), and N-acetyl aspartate (NAA) (Fig. 2A). The *N*-methyl groups of choline containing compounds resonate at 3.2 ppm in the MR spectra, Cr resonates at 3.0 ppm and the *N*-methyl group of NAA resonates at 2.0 ppm. Cho is a precursor for the neurotransmitter acetylcholine and for phosphatidylcholine and sphingomyelin, two common phospholipids in neuronal and glial membranes (25). NAA is relatively abundant in neural tissue and is believed to be involved in regulation of neuronal protein synthesis, myelin production, and the metabolism of several neurotransmitters such as aspartate and N-acetyl-aspartyl-glutamate (1). Both creatine and creatine phosphate contribute to the single creatine peak. Creatine serves as a reserve for high-energy phosphates in the cytosol of muscle and neurons and buffers cellular ATP/ADP reservoirs. The integrated areas of the ab-

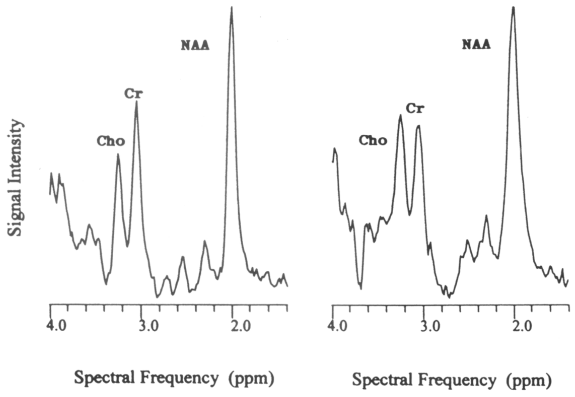

FIG. 2. A. Magnetic resonance spectrum, 2000/136 (repetition/echo time in msec), with the water signal suppressed, of a 3.4 cc brain tissue volume from a control animal (#37) and a 24-week ethanol exposed animal (#56). The Cho/Cr ratio (0.66) for the control animal is reflective of the group mean. The Cho/Cr ratio for the ethanol-exposed animal (0.95) was the highest observed ratio. choline (Cho), creatine (Cr), N-acetyl-aspartate (NAA). B. Baseline corrected spectra for the Cho, Cr, and NAA regions of the proton magnetic resonance spectra for the two animals presented in A. The solid line is the actual spectral data and the shaded line is the fit. The baseline was determined at constant ppm regions near the resonances for all the spectra and then fit to a linear equation. The baseline was subtracted from the spectrum before fitting was performed. Fitting was performed using a superposition of two resonances in the Gaussian equation for the Cho/Cr region and a single resonance Gaussian equation for the NAA region of the spectrum. The resonance areas were determined from the height and width resulting from the fit. choline (Cho), creatine (Cr), N-acetyl-aspartate (NAA).

sorption-mode resonances (peak areas) for Cho, Cr, and NAA were computed using Lorenzian/Gaussian peak-fitting software after automated baseline subtraction (Fig. 2B). Best fit was achieved using a 100% Gaussian distribution. Proton spectra were quantified by dividing the peak area of the metabolite of interest by the peak area of another metabolite in the spectrum providing relative rather than absolute measures of metabolite concentration. Because past studies have demonstrated that the creatine peak is relatively stable with various diseases, it is often used as a control value, with some limitations, to compare with changes seen in NAA and Cho (3).

Analysis

The MR images were reviewed for the presence of gross morphologic anomalies by two radiologists (EW, DWS) and a dysmorphologist (SKC), masked to the exposure history of the animals. Computer-aided volumetric analyses were not conducted. One-way analysis of variance (ANOVA) and Student-Newman-Keuls test for multiple comparisons were used to determine if significant differences in mean ^{1}H-MRS metabolite ratios and mean infant developmental impairment composite scores could be detected between the four ethanol exposure cohorts. Regression analysis was used to evaluate the relationship between ^{1}H-MRS metabolite ratios, gestational day of ethanol exposure, and composite scores of infant developmental impairment through 6 months of age.

RESULTS

Review of the MR images revealed no gross morphologic abnormalities of CNS structures among any of the animals. No gross differences in morphology or size of cerebral hemispheres, corpus callosum, brainstem, or cerebellum were visually detectable between the animals.

MRS revealed a statistically significant increase in the Cho : Cr ratio with increasing duration of in utero ethanol exposure (one-way ANOVA weighted linear trend: $F(3, 16) = 10.2, p = 0.006$ (Table 1, Fig. 3a). The 24-week ethanol cohort had a significantly higher mean Cho : Cr metabolite ratio relative to the control and 3-week ethanol cohorts (Student-Newman-Keuls multiple comparison test: $p < 0.05$). These results closely parallel the significant linear association observed between the infant developmental impairment scores and duration of ethanol exposure in which both the 6- and 24-week ethanol exposed cohorts differed significantly from the control group (one-way ANOVA weighted linear trend: $F(3, 16) = 6.8, p = 0.02$; Student-Newman-Keuls multiple comparison test: $p < 0.05$) (Fig. 3b). Although the increase in the Cho : Cr ratio could be due to an increase in Cho and/or a decrease in Cr, analyses of the ratios NAA : Cr and NAA : Cho strongly suggest that it is the Cho component that is changing with increasing duration of ethanol exposure, not the Cr.

No statistically significant associations were observed between the NAA : Cr and Cho : NAA metabolite ratios and duration of in utero ethanol exposure. Although the power to detect statistically significant associations was limited by the small number of animals in each group, the negative statistical results were supported by the lack of any pattern of association observed in the scatter plots (not illustrated).

Metabolite ratios did not vary with gender, age at the time of the MR evaluation, total dose of ketamine : xylazine/kg body weight, or gestational age at first dose of ethanol.

A scatter plot of the Cho : Cr ratios and the developmental impairment composite scores revealed a significant curvilinear relationship with 45% of the variance in the impairment score being explained by the Cho : Cr ratio ($r^2 = 0.45$; $F = 6.9$, $p = 0.006$). The curvilinear nature of the plot was dominated by the outcome of a single animal (animal #49) in the 6-week exposure cohort (identified by an asterisk in Fig. 4). This animal was the most developmentally delayed animal in the study and was the only animal with a Cho : Cr ratio greater than 2 SDs below the control mean. If the outlier is excluded from the analysis, the developmental impairment score increases linearly with increasing Cho : Cr ratio with 34% of the variance in the developmental outcome score being explained by the Cho : Cr ratio ($r^2 = 0.34$, $F = 8.6$, $p = 0.009$).

DISCUSSION

Results demonstrated brain Cho : Cr ratios detected by ^{1}H-MRS increased with increasing duration of in utero ethanol

TABLE 1

SUMMARY OF DESCRIPTIVE CHARACTERISTICS AND OUTCOMES ACROSS THE FOUR ETHANOL EXPOSURE COHORTS

Characteristics	Duration of Once-Per-Week Maternal Ethanol Exposure During Pregnancy			
	0 weeks	3 weeks	6 weeks	24 weeks
	(n = 6)	(n = 5)	(n = 5)	(n = 4)
Metabolite ratios, mean (SE)				
Cho : Cr*	0.66 (0.03)	0.67 (0.05)	0.72 (0.06)	0.85 (0.04)
NAA : Cr	2.01 (0.24)	1.63 (0.06)	1.95 (0.19)	2.07 (0.39)
Cho : NAA	0.34 (0.02)	0.41 (0.04)	0.37 (0.02)	0.44 (0.05)
Infant Developmental Outcome				
Scores†, mean (SE)	0.03 (0.02)	0.15 (0.05)	0.31 (0.09)	0.27 (0.04)
Female (n)	6	2	3	3
Age in years at time of MRI/^{1}H-MRS, mean (SE)	3.6 (0.2)	3.2 (0.2)	3.8 (0.1)	3.1 (0.3)
Age in days at first treatment dose, mean (SE)	— —	6.6 (1.1)	8.8 (1.2)	9.5 (1.3)
Ketamine : xylazine dose (mg/kg) mean (SE)	0.25 (0.05)	0.22 (0.03)	0.19 (0.01)	0.20 (0.03)

*One-way ANOVA weighted linear trend: $F(3, 16) = 10.2$, $p = 0.006$. Student-Newman-Keuls multiple comparison test: 24-week cohort differs from the control and 3-week cohort, $p < 0.05$. † One-way ANOVA weighted linear trend: $F(3, 16) = 5.8$, $p = 0.02$. Student-Newman-Keuls multiple comparison test: 6- and 24-week cohorts differ from the control group, $p < 0.05$. SE = Standard Error.

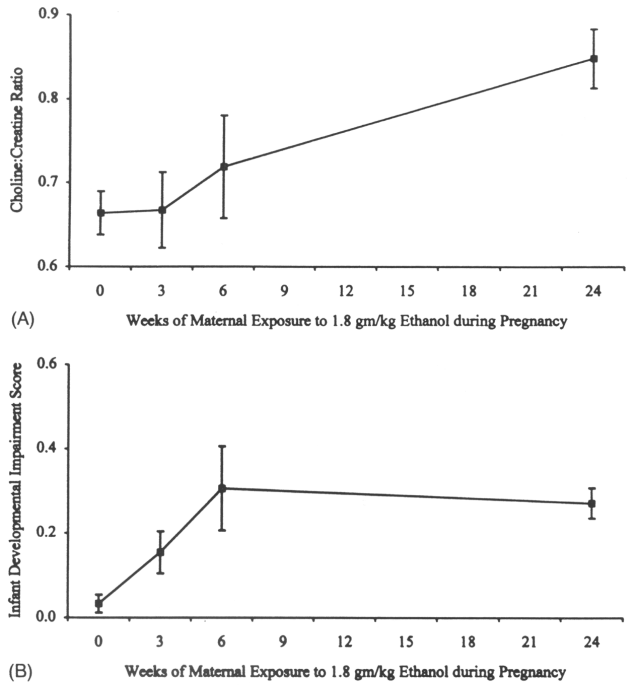

FIG. 3. A. Mean (±SE) brain choline : creatine ratios for the control, 3-week, 6-week, and 24-week ethanol exposure cohorts. The mean Cho : Cr metabolite ratio increased linearly with increasing duration of ethanol exposure (Oneway ANOVA weighted linear trend: $F(3, 16) = 10.2$, $p = 0.006$). B. Mean (±SE) infant developmental impairment score for the control, 3-week, 6-week, and 24-week ethanol exposure cohorts. The mean infant developmental impairment score increased linearly with increasing duration of ethanol exposure (one-way ANOVA weighted linear trend: $F(3, 16) = 6.8$, $p = 0.02$).

exposure, $F(3, 16) = 10.2$; $p = 0.006$, in this nonhuman primate model of fetal alcohol syndrome (FAS). These alterations occur in the absence of gross morphological abnormalities among live born animals (detectable by MR imaging). The Cho : Cr ratios were also observed to increase with increased cognitive and behavioral dysfunction in these animals ($r^2 = 0.45$; $F = 6.9$, $p = 0.006$). The observed increase in the Cho : Cr ratio is consistent with reports of elevated Cho : Cr ratios associated with various neurological insults and disease states (e.g., brain ischemia, brain tumors, multiple sclerosis, and Alzheimer's disease) (4,21,26,31,23). The absence of gross morphological abnormalities is consistent with observations in our previous study of ethanol teratogenicity in nonhuman primates (8). Morphological abnormalities such as agenesis of the corpus callosum have been reported in a few FAS case-series (9,19,22) but the prevalence appears to be quite low.

The Role of Choline and Detection by ^{1}H-MRS

Choline is a precursor for two important molecules, phosphatidylcholine (PtdCho) and acetylcholine (AcCho). Cho is present in membranes of all cells, where it constitutes the polar subunit of PtdCho, sphingomyelin, and plasmalogens. Within cholinergic neurons, Cho is also the precursor for the synthesis of AcCho (16). The rate of AcCho synthesis is regulated by the concentration of substrate Cho in cholinergic neurons. Choline acetyltransferase (CAT) catalyzes the synthesis of AcCho in the reaction: Cho + acetyl coenzyme A → AcCho + coenzyme A. AcCho is a neurotransmitter that is critical for many aspects of memory, cognition, and mood (13).

There remains uncertainty in the field of MR spectroscopy as to which of the choline containing compounds contribute to the 3.2 ppm peak. The total concentration of the major water soluble choline containing compounds including choline, glycerophosphocholine, phosphorylcholine, CDP-choline, AcCho, and choline-plasmalogen total to less than 1.6 mM (25). Conversely, lipid-soluble sphingomyelin and PtdCho occur in concentrations that are over 20 mM, but the proton spectrum of "normal" brain has little (if any) lipid signal because the phospholipids in cell membranes have limited mobility (37,15). It is believed that the choline peak seen in ^{1}H-MRS reflects all choline stores but is most likely dominated by sig-

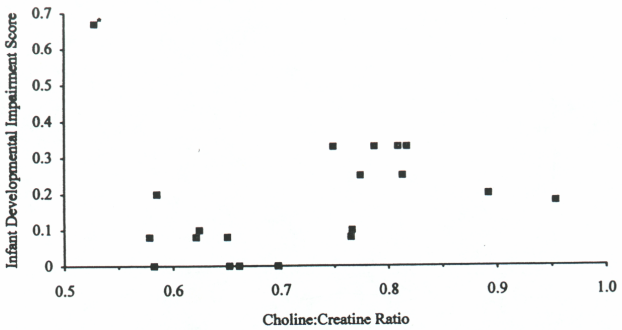

FIG. 4. Scatterplot of the the brain Cho/Cr ratios detected by ^{1}H-MRS and the developmental impairment composite scores. There is a significant curvilinear relationship with 45% of the variance in the impairment score being explained by the Cho : Cr ratio ($r^2 = 0.45$; $F = 6.9$, $p = 0.006$). The curvilinear nature of the plot was dominated by the outcome of a single animal in the 6-week exposure cohort (identified by an asterisk), which may be suggestive of a threshold effect. If the outlier is excluded from the analysis, the developmental impairment score increases linearly with increasing Cho : Cr ratio with 34% of the variance in the developmental outcome score being explained by the Cho : Cr ratio ($r^2 = 0.34$, $F = 8.6$, $p = 0.009$). choline (Cho) creatine (Cr).

nal from lipids being mobilized for membrane synthesis (e.g., brain tumor growth) or breakdown (e.g., demyelination observed in multiple sclerosis).

Cholinergic-based research in Alzheimer's Disease (AD) provides supportive evidence that the choline peak seen in ^{1}H-MRS may indeed be reflective of membrane destabilization. In AD, cortical AcCho and CAT levels are significantly reduced relative to age-matched controls (11,38). As noted, the rate of AcCho synthesis is regulated by the concentration of substrate Ch in cholinergic neurons. The decline of cortical AcCho in AD is attributed to the selective loss of cholinergic neurons, particularly from the cholinergic pathway projecting from deep nuclei located in the septum near the diagonal band of Broca to the hippocampus and from the nearby basal nucleus of Meynert to the cerebral cortex (10) (Fig. 5). Wurtman et al. (39) hypothesized that Cho deprived cholinergic neurons catabolize their own membranes ("autocannabalism") to free-up Cho for AcCho synthesis. Wurtman et al. suggest that this dual use of Cho for membrane and neurotransmitter synthesis could make AcCho producing cells particularly vulnerable to alterations in Cho levels. In a recent ^{1}H-MRS study, Meyeroff et al. (23) observed significantly higher Cho/Cr signals in patients with AD relative to elderly controls. Cho/Cr was 37% higher ($p = 0.0002$) in the mesial gray matter of the centrum semiovale and 23% higher ($p = 0.05$) in adjacent lateral voxels located in a predominantly white matter region of the posterior cortex. The authors note the consistency of their observations with reports in the AD literature document-

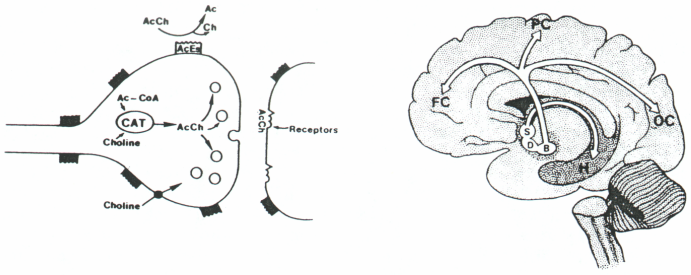

FIG. 5. Cholinergic pathways innervating cortex. The cholinergic neuronal cell bodies of the basal forebrain located in the nucleus basilis of Meynert (B), the diagonal band of Broca (D), and the medial septal nucleus (S) send axons that innervate the entire cortex including the frontal (FC), parietal (PC), and occipital (OC) cortex, as well as the hippocampal formation (H). (Reprinted with permission by Coyle et al., 1983).

ing membrane degradation effects due to increased phospholipid turnover (28,29) and defective membrane lipid compositions associated with membrane bilayer destabilization (17). As Meyerhoff et al. state, these observations are unified by Wurtman's "autocannabalism" theory on the pathogenesis of AD.

Depletion of Cholinergic Nuclei in a Mouse Model of FAS

Although limited work has been focused on the cholinergic system in FAS research, a recent study in mice has confirmed that in utero ethanol exposure can cause severe depletion of cholinergic nuclei (32). In that study, C57B1/6J mice were given two doses of ethanol (2.9 g/kg maternal body weight per dose, 500–600 mg/dl maternal peak blood alcohol concentration) on GD 7. In the mildly affected brains of GD 18 fetuses, fewer cells were immunoreactive for CAT in the medial septal nucleus and the vertical and horizontal nucleus of the diagonal band of Broca. In the severely affected brains, cells immunoreactive to CAT were totally absent. The severely affected mice had craniofacial anomalies consistent with those observed in humans with FAS. Schambra reports that without the projections of cholinergic neurons of the medial septal nucleus and the vertical nucleus of the diagonal band of Broca to the hippocampus, memory deficits as well as difficulty in inhibiting unwanted behaviors can be expected, as is reported to occur in FAS humans.

Although Schambra (32) and Sulik (34,35) have identified GD 7 in the mouse (Stage 9 of embryonic development, gastrulation) as a critical stage when acute exposure to ethanol can result in medial forebrain anomalies and FAS-like facial dysmorphia, the outcomes observed in this non human primate study cannot be isolated to a single stage of development because ethanol was administered weekly. There is one event, however, that was observed in this study that not only suggests that timing of exposure may be an important factor related to outcome but also provides a link between the outcomes observed in Schambra's study and the outcomes observed in this study. Schambra (32) and Sulik (35,35) report a continuum of ethanol induced teratogenic damage with holoprosencephaly representing the severe end of the spectrum. Sulik (36) goes on to speculate that severe cases of FAS represent the mild end of the holoprosencephaly spectrum. In this group of non human primates, one ethanol exposed animal was born with holoprosencephaly (33), an event that has never before been reported in the non human primate literature. Only one other animal (animal #56) in this MRI/S study had a weekly dosing pattern that was identical in timing (GDs 12, 21, 26 . . .), level, and duration to the holoprosencephalic animal. That animal had the highest Cho : Cr ratio of the group, a ratio that was 4.8 SDs higher than the control mean. Stage 9 of embryonic development in man (30) and macaque is estimated to occur at 20 ± 1 days postovulation.

Area Localized for ^{1}H-MRS

The majority of cortical cholinergic innervation is derived from nerve cells in the basal forebrain (20). The primary source of cortical cholinergic innervation in the rat originate from neurons in the ventral and medial aspects of the *globus pallidus*, extend into the hypothalamus and range rostrally to include the diagonal band of Broca and the medial septal nucleus (12). These areas correspond to the areas of cholinergic nuclei depletion observed in the FAS mouse model following in utero ethanol exposure (32). Comparative neuroanatomic studies indicate that the major part of this cholinergic system in primates is located in the nucleus basilis of Meynert (22) (Fig. 5), an area that was incorporated in the 3.4 cc voxel localized for ^{1}H-MRS in this primate study.

Based on the mechanism of cholinergic membrane vulnerability postulated by Wurtman et al. (39) one could speculate that the increased Cho : Cr ^{1}H-MRS signal ratios observed in this study may be associated with membrane breakdown. If AcCho is deficient, as might be expected based on the type of cognitive/behavioral impairment which is characteristic of patients with FAS (and is confirmed to be present in these nonhuman primates), breakdown of cholinergic neuron membranes could serve as a compensatory measure to free up Cho for AcCho synthesis. As demonstrated by Tunggal et al. (37), choline from catabolism of membrane phospholipids might considerably contribute to the AcCho neurotransmitter pool of the CNS. If cholinergic membranes were breaking down, one would expect to observe elevated Cho : Cr ^{1}H-MRS signals.

Interestingly, the only animal that deviated from the pattern of increased Cho : Cr signal with increased cognitive impairment was animal #49, the animal with the most profound cognitive and behavioral impairment and the only live born animal with minor facial dysmorphia. One could speculate that this animal may have sustained a level of damage that was beyond that of the other animals, perhaps severe enough to result in depletion of cholinergic nuclei. In such case, compensatory measures such as membrane breakdown would be less successful at achieving adequate AcCho levels and would result in a lower Cho : Cr MRS signal, as was observed. Ongoing neuroanatomical and neurochemical studies may shed light on the apparent uniqueness of this individual animal.

In conclusion, the association observed between brain Cho : Cr ratios and in utero ethanol exposure suggest a role for ^{1}H-MRS in elucidating mechanisms of ethanol teratogenicity. There may further be diagnostic benefits derived from the metabolic information available from ^{1}H-MRS in evaluation of FAS. These findings add further weight to the developing body of knowledge that purport that behavioral abnormalities can be attributable to prenatal exposure to ethanol in utero without evidence of microcephaly or structural aberration at the resolution level of CT or MR imaging. To our knowledge, this is the first reported association between in utero ethanol exposure and cranial Cho : Cr ratios detected by ^{1}H-MRS. Although further study is required to confirm this association, the dose-response nature of the association and documented cholinergic vulnerability in other animal models of FAS lend credence to this observed association.

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A Fetal Alcohol Syndrome Screening Tool

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The purpose of this study was to derive a multivariate, quantitative case definition of the fetal alcohol syndrome (FAS) facial phenotype from a dysmorphologist-derived gold standard and use it to develop an effective screening tool for identification of children at risk for FAS. The facial and physical features of a racially mixed group of children (0.2–10.0 years of age), evaluated by a single dysmorphologist in the University of Washington FAS Clinic, were used to determine which feature or set of features best differentiated between children with and without a diagnosis of FAS. The study population was divided into two groups balanced on gender, age at examination, race, diagnosis, and date of examination. Group 1 was used to identify the most differentiating feature(s), and group 2 was used to validate the differentiating capability of the feature(s). Group 1 included 97 children (20 with FAS and 77 without FAS). Group 2 included 97 children (19 with FAS and 78 without FAS). Discriminant analysis identified smooth philtrum, thin upper lip, and short palpebral fissures as the cluster of features that best differentiated children with and without FAS based on the discriminant function [D = 1.7953086 + 0.8116083 (thin upper lip) + 2.6411562 (smooth philtrum) − 3.4073780 (% predicted right palpebral fissure length)]. Patients with a D-score ≥ 1.5 were classified as at-risk for FAS (screen positive). Using this cut-off value for the D-score, children in group 1 were classified with 100% sensitivity (20 of 20 true positives) and 90.0% specificity (70 of 77 true negatives). The children in group 2 were classified with 100% sensitivity (19 of 19 true positives) and 87.3% specificity (68 of 78 true negatives). Across all 194 patients, sensitivity was 100% [95% confidence interval (97–100)] and specificity was 89% [95% confidence interval (85 to 93)]. Seventy-one percent (n = 12) of the 17 false-positives had a true classification of possible fetal alcohol effects. Sensitivity and specificity were unaffected by race, gender, and age through 10 years. This screening tool is effective at differentiating children with and without FAS as diagnosed by a single dysmorphologist (S.K.C.) at the University of Washington FAS Clinic. Assessment of diagnostic interrater agreement between trained dysmorphologists and testing in other clinic populations will be needed to assess the tool's external validity.

Key Words: Fetal Alcohol Syndrome, Screening.

FETAL ALCOHOL syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. FAS is characterized by cognitive/behavioral dysfunction, a unique cluster of minor facial anomalies, and is often accompanied by growth deficiency. FAS is the leading known cause of mental retardation in the Western World,[1] with an estimated incidence of 1–3 per 1000 live births.[2] Not all individuals exposed to alcohol during gestation have FAS. Individuals who have been exposed to alcohol in utero and present with cognitive/behavioral disabilities, but do not have the characteristic FAS facial appearance, are often classified as having possible fetal alcohol effects (PFAEs). Unlike FAS, PFAE is not a recognized medical diagnosis, for in the absence of the FAS facial phenotype, the cognitive/behavioral dysfunction cannot be definitively linked to the prenatal alcohol exposure in any one individual.[3] The cognitive/behavioral disabilities associated with PFAE are as severe as those associated with FAS. The incidence of PFAE is unknown, but is speculated to exceed that of FAS.

Individuals with FAS endure life-long disabilities. These disabilities are often compounded by secondary disabilities, such as low self-esteem, depression, aggression, school failure, and juvenile detention when the syndrome goes undiagnosed. These secondary disabilities come at a high cost to the individual, their family, and society, and can be reduced by early diagnosis and receipt of appropriate intervention.

Failure to diagnose FAS stems in large part from the difficulty inherent in making the diagnosis. Although confirmation of central nervous system dysfunction and growth deficiency are relatively straightforward clinical procedures, diagnosis of the FAS facial phenotype is less straightforward. An accurate diagnosis of the facial phenotype is best achieved by a trained dysmorphologist. Dysmorphologists typically use a "gestalt" approach to diagnosing FAS. The gestalt (or general clinical impression) approach focuses on the whole rather than the parts. It is qualitative rather than quantitative in nature. Use of a gestalt approach to pattern recognition is not unique to dysmorphologists. Anyone who has recognized an individual as having Down's syndrome is using a gestalt method. The phenotypic expression of Down's syndrome is sufficiently distinct that one need not measure the facial features to render an accurate phenotypic diagnosis. The gestalt method is a well-accepted standard of syndrome diagnosis that can be conducted with sufficient accuracy and reproducibility when performed by trained professionals.[4] The gestalt method becomes less accurate and reproducible when conducted by untrained individuals trying to diagnose a birth defect syndrome like FAS. Lack of diagnostic accuracy not only affects the individual patient, but also curtails public health screening and surveillance efforts aimed at tracking the incidence/prevalence of FAS; tracking that is paramount to service provision and primary prevention.[5]

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The definition of a gold standard is "a method, procedure, or measurement that is widely accepted as being the best available. Often used to compare with new methods."[6] Although there is no officially recognized gold standard for the diagnosis of FAS, the gestalt method of diagnosis performed by a trained dysmorphologist was selected to serve as the gold standard for this study. The purpose of this study was to derive a case definition of the FAS facial phenotype from this gold standard and use it to develop an effective screening tool for identification of children at risk for FAS in the University of Washington FAS Clinic.

METHODS

Overview

This study was conducted at the Centers for Disease Control-sponsored FAS Clinic at the Center of Human Development and Disabilities at the University of Washington (Seattle, WA). The FAS Clinic serves a large, racially mixed patient population, all of whom are diagnosed by a single dysmorphologist (S.K.C.) with recognized expertise in FAS. The prevalence of FAS in the patient population is 20%. All patients from birth to 10.0 years of age, evaluated in the Clinic between January 1993 (the month the Clinic opened) and January 1995, were eligible for entry into the study (n = 194). The age range was restricted to maximize the accuracy of the FAS diagnosis, because the face often becomes less specifically anomolous after puberty. The 194 patients were randomly divided into two groups (n = 97 per group) balanced on age at examination, gender, race, diagnosis, and date of examination. A discriminant analysis was used to identify the facial/physical feature(s) that best differentiated the patients with and without FAS in group 1. The multivariate discriminant equation generated by the discriminant analysis served as both the FAS phenotypic case definition and the method (or screening tool) by which risk of FAS was assessed among patients in group 2. Application of the screening tool to group 2 served as an opportunity to test (or validate) the tool's performance among the University of Washington FAS Clinic patients.

Referral Population

The University of Washington FAS Clinic sees patients of all ages from all over the State of Washington. The geographic and racial distribution of the Clinic's patient population approximates the State's population. Referred patients typically have cognitive/behavioral dysfunction and a known or suspected history of in utero alcohol exposure. A small subset of the patients are referred solely on the basis of a history of in utero alcohol exposure. This subset tends to be infants awaiting foster/adoptive care.

Diagnosis

All patients were diagnosed by a trained dysmorphologist (S.K.C.) using a "gestalt" method of diagnosis (described herein). Patients were classified into 1 of 4 categories defined as follows:

FAS: Reported in utero alcohol exposure, CNS dysfunction, distinct presentation of the FAS facial phenotype, with or without documented growth deficiency.

AFAS (atypical fetal alcohol syndrome): Reported in utero alcohol exposure, CNS dysfunction, mild presentation of the FAS facial phenotype, with or without documented growth deficiency.

PFAE: Reported in utero alcohol exposure, CNS dysfunction, absence of the FAS facial phenotype, with or without documented growth deficiency.

Other: In utero alcohol exposure reported or suspected, but no diagnosis of FAS, AFAS, or PFAE was made because of the absence of both FAS-like facial anomalies and CNS dysfunction.

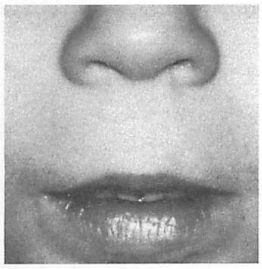
These classifications served as the "gold standard" (or true) classifications from which to compare the predicted classifications generated by the screening tool.

Measures

All patients evaluated in the FAS Clinic receive a comprehensive evaluation by a team of professionals, including a pediatrician/dysmorphologist (S.K.C.), a developmental pediatrician, a geneticist, a clinical psychologist, an educational psychologist, an educational liaison, a communication specialist, an occupational therapist, a social worker, and a public health nurse. Each patient receives a complete physical and dysmorphic examination. The physical and facial measures recorded and entered into this analysis are listed and defined in Table 1. The phenotypic

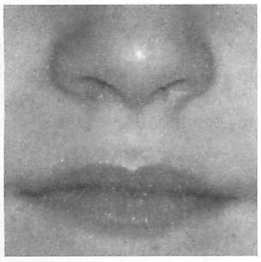
Table 1. Physical and Facial Measures Collected at the Time of Clinical Evaluation

Measure	Description
Eyes and eyebrows	
Palpebral fissure length	Distance between outer and inner canthi for right and left eyes (cm)
Inner canthal distance	Distance between right and left inner canthi (cm)
Clown eyebrows	High-arched eyebrows; (definitely, somewhat, or not present)
Ptosis	Drooping of the eyelid(s); (definitely, somewhat, or not present)
Epicanthal folds	Lateral extension of the skin of the nasal bridge down over the inner canthus; (definitely, somewhat, or not present)
Midface	
Nose length	Distance from inner canthus to the subnasion (cm)
Midface height	Distance from inner canthus to the lower border of the upper lip (cm)
Flat nasal bridge	(Definitely, somewhat, or not present)
Hypoplastic midface	Flat midface; (definitely, somewhat, or not present) (Fig. 2)
Mouth	
Smooth philtrum	Vertical ridges between the upper lip and the subnasion; (definitely, somewhat, or not present) (Fig. 1)
Thin upper lip	(Definitely, somewhat, or not present) (Fig. 1)
Abnormal palate	(Definitely, somewhat, or not present)
Palmar creases	
Hockey stick creases	(Present, absent)
Body measures	
Height	Height percentile for age and gender
Weight	Weight percentile for age and gender
OFC	% predicted occipital frontal circumference (OFC) for age and gender



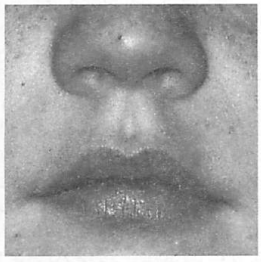
Definitely smooth philtrum and definitely thin upper lip

Likert scale 2



Somewhat smooth philtrum and somewhat thin upper lip

Likert scale 1



Well defined philtrum and full upper lip

Likert scale 0

Fig. 1. Illustration of the 3-point Likert scale used to rank smooth philtrum and thin upper lip.

expression of several facial features are ranked on a 3-point Likert scale (definitely present, somewhat present, and not present). Pictorial examples of each of these rankings for thin upper lip, smooth philtrum, and hypoplastic midface are presented in Figs. 1 and 2. Right and left palpebral fissure lengths were measured for all patients and were found to be identical in 85% of the patients and within 0.1 cm of one another in 97% of the patients. Therefore, the right palpebral fissure length was arbitrarily selected for entry into the analysis. Several of the measures were transformed to age and/or sex-standardized measures as follows. Right palpebral fissure length, inner canthal distance, and occipital frontal circumference were converted to percent predicted measures for age and/or gender using formulas derived from plots of normal values published in Hall et al.[7] The formuli used to compute percent predicted palpebral fissure length for age were:

Predicted mean palpebral fissure length (mm)

$$= 19.154 + 3.2385\,(\text{age}) - 0.6242\,(\text{age}^2) + 0.0689\,(\text{age}^3) - 0.0037\,(\text{age}^4) + 0.000076\,(\text{age}^5)$$

where age is measured in years and is between 0 and 16 years.

Percent predicted right palpebral fissure length (PFL)

$$= \text{observed right PFL/predicted mean PFL}.$$

Height (cm) and weight (kg) were converted to height and weight centiles adjusted for age and gender using EPI-INFO, public-domain software distributed by the Centers for Disease Control and Prevention.[8] Norms for nose length and midface height were not available; therefore, the nose/midface ratio was used rather than the absolute measure of each feature.

Discriminant Analysis and Computation of Sensitivity and Specificity

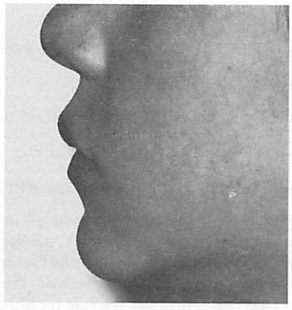
Discriminant analysis with step-wise variable selection (Wilk's lambda; F to enter = 3.84, F to remove = 2.71) was used to identify the physical features that best differentiated patients with and without FAS/AFAS. Prior probability of FAS/AFAS was computed from the prevalence in the study sample. The unstandardized canonical discriminant function coefficients were computed to derive the formula for calculation of each patient's discriminant score (or D-score). The D-score was used to classify whether or not a patient was at risk for FAS/AFAS. The D-score distributions for the patients with and without FAS/AFAS in group 1 were plotted to identify the D-score cut-off value that resulted in the highest sensitivity and specificity with priority given to maximizing the sensitivity. Sensitivity is the proportion of patients with FAS/AFAS who are correctly screened positive for FAS/AFAS. Specificity is the proportion of patients without FAS/AFAS who are correctly screened negative for FAS/AFAS.

D-scores for patients in group 2 were computed using the discriminant equation derived from group 1. Patients with D-scores ≥ 1.5 were classified as at-risk for FAS/AFAS (screen positive). Patients with D-scores < 1.5 were classified as not at risk for FAS/AFAS (screen negative). The sensitivity and specificity of the discriminant function (or screening tool's) performance were computed for group 2 as previously described.

RESULTS

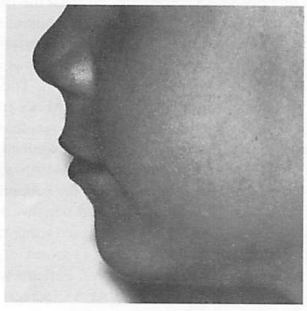
The total population of 194 patients, 0.2–10.0 years of age, was divided into two groups ($n = 97$ per group) and successfully balanced on age at examination, gender, race, diagnosis, and date of examination (Table 2). Selected physical and facial characteristics of all patients are presented by diagnostic category (FAS, AFAS, PFAE, and Other) in Table 3. As would be expected, the presence of many of the individual physical and facial characteristics decrease as one progresses from the diagnostic classification of FAS, AFAS, PFAE, to Other. No two children with FAS had an identical pattern of facial features. The variation of phenotypic expression across the 27 children with FAS is displayed in Fig. 3.

In group 1, step-wise discriminant analysis selected hypoplastic midface, smooth philtrum, and thin upper lip as the three characteristics that best differentiated the patients with and without FAS/AFAS (sensitivity = 100%, specificity = 89.4%). Palpebral fissure length and hypoplastic midface were observed to be correlated (Spearman rank correlation coefficient = -0.37, $p < 0.000$) (Fig. 4). In an effort to identify features that could be most accurately recorded and were least influenced by race, palpebral fissure length was substituted for hypoplastic midface in the model without any loss of discrim-



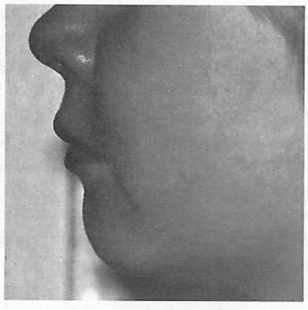
Definitely Hypoplastic Midface

Likert Scale = 2



Somewhat Hypoplastic Midface

Likert Scale = 1



Well Developed Midface

Likert Scale = 0

Fig. 2. Illustration of the 3-point Likert scale used to rank hypoplastic midface.

inating power. Because a flattened midfacial profile is a "normal" characteristic in some races (including Asian and American Indian), inclusion of this feature would limit the positive predictive value of the tool. Discrimination was best when smooth philtrum and thin upper lip were dichotomized as 0 = not present, 1 = somewhat/definitely present. The discriminant equation for computation of the D-score was:

$$D = 1.7953086 + 0.8116083\ (\text{thin upper lip}) + 2.6411562\ (\text{smooth philtrum}) - 3.4073780\ (\%\ \text{predicted right palpebral fissure length}).$$

This discriminant equation served as the quantitative, multivariate, phenotypic case definition for FAS/AFAS. A D-score cut-off value of ≥1.5 = at-risk for FAS/AFAS resulted in the maximum sensitivity (100%; 20 of 20 correctly classified as having FAS/AFAS) and specificity (90.9%; 70 of 77 correctly classified as not having FAS/AFAS) for patients in group 1. The discriminant equation classified the FAS/AFAS risk of group 2 patients with 100% sensitivity (19 of 19 correctly classified as FAS/AFAS) and 87.2% specificity (68 of 78 patients correctly classified as not having FAS/AFAS).

Across groups 1 and 2 combined, the discriminant formula classified the patients' FAS/AFAS risk status with 100% sensitivity (39 of 39 true positives) and 89% specificity (138 of 155 true negatives). The 95% confidence intervals for the estimate of sensitivity was 97–100%. The 95% confidence interval for the estimate of specificity was 85–93%. The distribution of D-scores for all 194 patients with and without FAS/AFAS is illustrated in Fig. 5. Seventeen of the 197 patients (9%) were classified as false-positives. Twelve of the 17 false-positive classifications (71%) had a true classification of PFAE. Selected characteristics of these 17 patients are presented in Table 4. Misclassification was not associated with race, gender, or age. Race, gender, and age had little influence on the sensitivity and specificity, as illustrated in Table 5. Three of the 194 patients had other syndrome diagnoses: Marfan syndrome, William's syndrome, and Schprintzen's syndrome. None of these patients received a diagnosis of FAS/AFAS in the FAS Clinic, and all three were correctly screened as not having FAS/AFAS.

Table 2. Illustration of the Balance Achieved on Selected Characteristics between Groups 1 and 2

Characteristic	Group 1 (n = 97)	Group 2 (n = 97)
Age at time of exam [mean (SD)]	5.3 (2.6)	5.2 (2.6)
Females [n (%)]	43 (44)	43 (44)
Race [n (%)]		
Caucasian	46 (47)	47 (48)
African American	11 (11)	7 (7)
American Indian	20 (21)	19 (20)
Alaskan Native	4 (4)	3 (3)
Asian	0 (0)	1 (1)
Other	16 (17)	20 (21)
Diagnosis [n (%)]		
FAS	14 (14)	13 (13)
AFAS	6 (6)	6 (6)
PFAE	57 (59)	56 (58)
Other	20 (21)	22 (23)

Table 3. Physical and Facial Characteristics among the Different Diagnostic Groups

Characteristic	1 FAS (n = 27)	2 AFAS (n = 12)	3 PFAE (n = 113)	4 Other (n = 42)	Total (n = 194)	Statistic	p value and group contrasts
Age at exam [mean (SD)]	5.1 (2.5)	5.2 (2.8)	5.4 (2.6)	4.9 (2.6)	5.2 (2.6)	F, 0.4	0.74
Female [n (%)]	10 (37)	7 (58)	48 (43)	21 (50)	86 (44)	χ^2, 2	0.52
Race [n (%)]							
Caucasian	13 (48)	5 (42)	56 (50)	19 (45)	93 (48)	χ^2, 9	0.89
African American	4 (15)	1 (8)	8 (7)	5 (13)	18 (9)		
American Indian	4 (15)	4 (33)	23 (20)	8 (19)	39 (20)		
Alaskan Native	1 (4)	1 (8)	4 (4)	1 (2)	7 (4)		
Asian	0 (0)	0 (0)	0 (0)	1 (2)	1 (1)		
Other	5 (18)	1 (8)	22 (19)	8 (19)	36 (18)		
Parity of index child							
Mean (SD)	3.5 (2.1)	3.6 (1.9)	2.7 (1.6)	2.3 (1.4)	2.7 (1.7)	FL, 8	0.006
n*	22	9	103	37	171	SNK	1 ≠ 4
Birth weight [kg, mean (SD)]	2.7 (0.8)	2.8 (0.5)	3.1 (0.7)	2.9 (0.5)	3.0 (0.7)	F, 3	0.03
n	17	9	89	34	149	SNK	1 ≠ 3
Gestational age [(wks), mean (SD)]	36.2 (4.0)	37.9 (3.0)	38.2 (2.7)	37.9 (2.3)	37.9 (2.8)	FL, 3	0.07
n	15	8	65	29	117		
Weight for age centile [mean (SD)]	24 (24)	54 (34)	52 (31)	46 (30)	47 (32)	FL, 8	0.002
						SNK	1 ≠ 2, 3, 4
Height for age centile [mean (SD)]	26 (28)	39 (32)	43 (32)	39 (28)	40 (31)	FL, 3	0.09
% predicted OFC	0.97 (0.04)	1.00 (0.03)	0.99 (0.07)	0.99 (0.03)	0.99 (0.03)	FL, 3	0.08
% Predicted right palpebral fissure length [mean (SD)]	0.81 (0.05)	0.87 (0.09)	0.89 (0.08)	0.89 (0.09)	0.88 (0.09)	FL, 16	0.0001
						SNK	1 ≠ 2, 3, 4
Ptosis [n (%)]	7 (26)	5 (42)	8 (7)	2 (5)	22 (11)	MH, 12	0.0005
Clown eyebrows [n (%)]	7 (26)	0 (0)	7 (6)	0 (0)	14 (7)	MH, 12	0.0005
Epicanthal folds [n (%)]	14 (52)	7 (58)	37 (33)	19 (45)	76 (39)	MH, 0.1	0.72
Hypoplastic midface [n (%)]	24 (89)	10 (91)	26 (23)	8 (19)	68 (35)	MH, 48	<0.0000
Abnormal palate [n (%)]	11 (41)	2 (17)	21 (19)	9 (21)	41 (21)	MH, 8	0.005
Nose length/midface height [mean (SD)]	0.64 (0.08)	0.61 (0.03)	0.65 (0.06)	0.64 (0.05)	0.64 (0.06)	F, 2	0.12
Smooth philtrum [n (%)]	27 (100)	12 (100)	16 (14)	6 (14)	61 (31)	MH, 80	<0.0000
Thin upper lip [n (%)]	25 (93)	11 (92)	35 (31)	11 (26)	82 (42)	MH, 41	<0.0000
Hockey stick palmar creases [n (%)]	7 (27)	5 (42)	26 (25)	6 (14)	44 (23)	MH, 3	0.09

FL, F statistic—one-way analysis of variance test for weighted linear trend; F, F statistic—one-way analysis of variance; SNK, Student-Newman-Keuls multiple comparison test used to identify which group pairs differed at $p < 0.05$; MH, Mantel-Haenszel test for linear association across the diagnostic categories; χ^2, Pearson χ^2 test; OFC, occipital frontal circumference.

* Sample size is reported when they differ from the total sample size in each diagnostic group.

DISCUSSION

This study has demonstrated that children with and without FAS, as diagnosed by a single dysmorphologist (S.K.C.) at the University of Washington FAS Clinic, can be consistently differentiated based on the combined level of expression of three facial features: palpebral fissure length, philtrum smoothness, and upper lip thinness. The clinical population included males and females, 0.2 and 10 years of age, from several racial backgrounds, including Caucasian, African, American, American Indian, Alaskan Native, Asian, Hispanic, and Mexican American. The screening tool performed with a high level of accuracy, with minimal influence by gender, race, and age up to 10 years. The patient population was purposely restricted to individuals ≤10.0 years of age, because it is well documented that the FAS facial features often change with the onset of adolescence.[9–12]

The development of this FAS screening tool represents a potential turning point in our ability to reliably and effectively screen children at risk for FAS. Emphasis was placed on identifying discriminating facial features for several reasons. First, they can be readily measured by individuals other than fully trained dysmorphologists/clinical geneticists. Second, unlike CNS dysfunction and growth deficiency, the facial phenotype is the only aspect of the syndrome that is specific to FAS, thereby serving as an ideal screening factor. Third, the facial features captured in this screening tool can be readily assessed from facial photographs, opening up the possibility of conducting population-based screening and/or surveillance with relative ease and efficiency. A recently completed pilot study (n = 20) assessing the feasibility of developing an FAS screening tool using facial features captured from photographs resulted in 100% sensitivity and specificity (Astley and Clarren, unpublished data).

This study represents the first step in the development of this tool. The next step is to test its performance in other clinical and population-based samples. Application in a variety of populations will serve to further validate its sensitivity and specificity, as well as document it's predictive value positive (PV+) and negative (PV−) in the field. The PV+ is the probability that a person with a positive FAS screening result does indeed have FAS. The PV− is the probability that a person with a negative FAS screening result does not have FAS. PV+ and PV− are dependent on the sensitivity and specificity of the screening tool, as well as the prevalence of FAS in the population being screened.

The performance of this screening tool is dependent on the accuracy and precision with which morphometric data is collected and to that end, standardized methods of data collec-

tion must be established[13] and intra- and interrater reliability will need to be documented. The gold standard selected for use in this study was the clinical judgment of a single dysmorphologist (S.K.C.). Because a formal assessment of diagnostic agreement between trained dysmorphologists has never been conducted, the results of this study reflect the clinical judgment of this dysmorphologist.[14]

One of the purposes of this study was to derive a case definition of the FAS facial phenotype using the gestalt method of diagnosis as the gold standard. The FAS facial phenotype is characterized by a cluster of minor facial anomalies that include small palpebral fissures, a flat midface, a smooth philtrum, and a thin upper lip.[15] But how small do the palpebral fissures have to be? How thin must the upper lip be? How is thinness measured? What combination of features must be present to establish a phenotypic diagnosis? Must all features be present? Are four of five sufficient? These are questions continually being asked by clinicians and researchers faced with diagnosing or classifying individual patients. Because the gestalt method of diagnosis does not rely on direct measurement of these features, answers to these questions have never been available. Without answers to these questions, establishment of an FAS phenotypic case definition has remained elusive. By quantitatively recording the phenotypic expression of facial features in our patient population, discriminant analysis was able to derive a multivariate, quantitative case definition that, for the first time, provides answers to these questions. Establishment of a case definition will provide a consistency of diagnosis across clinical and research

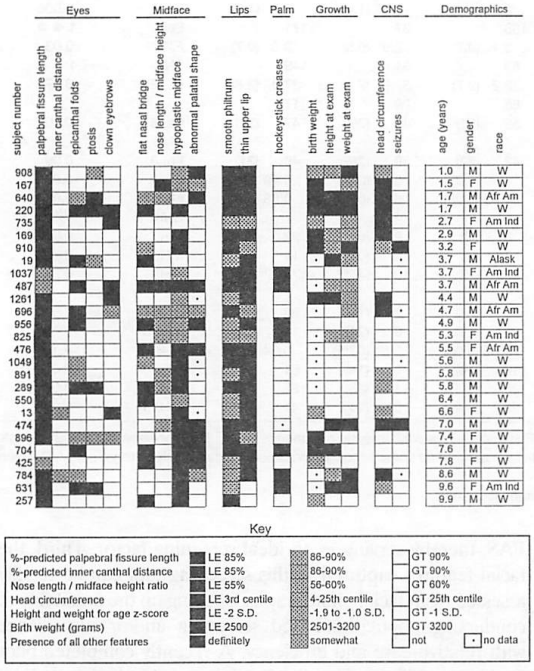


Fig. 3. Variability of selected facial and physical features among the 27 children with FAS. LE, less than or equal to; GT, greater than; W, White; Afr Am, African American; Am Ind, American Indian; Alask, Alaskan Native.

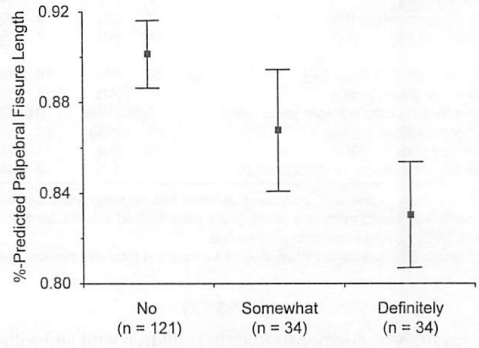


Fig. 4. Correlation between percent predicted right palpebral fissure length for age and midface hypoplasia among the 194 children (0.2–10.0 years of age). The mean and 95% confidence intervals are displayed. Mean percent predicted right palpebral fissure length ± 1 SD for each midface group are as follows: no (0.90 ± 0.08); somewhat (0.87 ± 0.08), and definitely (0.83 ± 0.07). One-way analysis of variance, linear trend, $F = 22.9$, $p < 0.0000$.

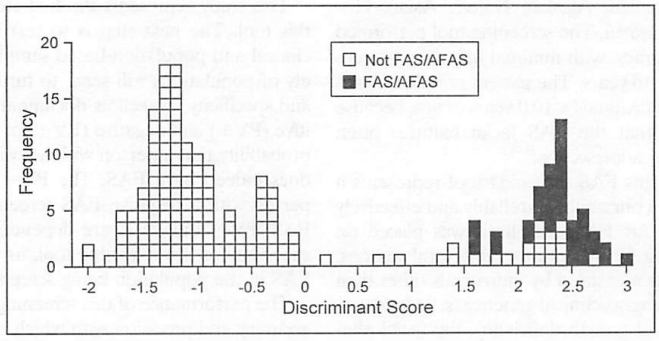


Fig. 5. Distribution of discriminant scores among the patients with (■) and without (□) FAS/AFAS across study groups 1 and 2 combined ($n = 194$).

Table 4. Selected Characteristics of the 17 Patients without FAS/AFAS Who Were Screened Positive for FAS/AFAS by the FAS Screening Tool

Diagnosis	Gender	Race	Age (yr)	Thin lip	Smooth philtrum	% Predicted palpebral fissure length for age	Discriminant score
PFAE	M	Am Ind	6.8	No	Somewhat	85	1.55
PFAE	F	Wh	6.6	No	Somewhat	77	1.80
PFAE	F	Wh	1.7	No	Somewhat	73	1.94
PFAE	F	Wh	6.0	Yes	Yes	93	2.07
PFAE	M	Wh	7.0	Yes	Somewhat	92	2.12
Other	M	Am Ind	9.9	Yes	Somewhat	91	2.15
PFAE	F	Wh	8.8	Somewhat	Somewhat	89	2.21
PFAE	F	Wh	2.9	Yes	Somewhat	89	2.22
Other	F	Wh	6.4	Yes	Yes	89	2.22
Other	M	Afr Am	4.7	Somewhat	Yes	88	2.25
PFAE	F	Wh	7.5	Yes	Somewhat	87	2.27
PFAE	M	Wh	7.4	No	Somewhat	62	2.33
PFAE	M	Wh	4.3	Somewhat	Somewhat	85	2.35
PFAE	M	Wh	7.1	Somewhat	Somewhat	84	2.38
Other	M	Wh	5.3	Yes	Somewhat	83	2.41
PFAE	M	Wh	8.3	Somewhat	Somewhat	83	2.43
Other	M	Wh	9.2	Yes	Somewhat	74	2.72

Subjects are listed in order of increasing discriminant score. Other, not FAS, AFAS, or PFAE; Am Ind, American Indian; Wh, White; Afr Am, African American; discriminant score, computed using the formula presented in the text.

Table 5. Sensitivity and Specificity of the FAS Screening Tool Stratified by Gender, Age, and Race, among Groups 1 and 2 Combined

Characteristic	*n*	Sensitivity (%)	95% CI	(*n*/*n*)	Specificity (%)	95% CI	(*n*/*n*)
Males	108	100	(96–100)	(22/22)	87	(80–94)	(75/86)
Females	86	100	(95–100)	(17/17)	90	(83–97)	(62/69)
Young (0–5.0 yr)	92	100	(96–100)	(20/20)	93	(87–99)	(67/72)
Old (5.1–10.0 yr)	102	100	(96–100)	(19/19)	84	(76–92)	(70/83)
Caucasian	93	100	(95–100)	(18/18)	84	(76–92)	(63/75)
African American	18	100	(91–100)	(5/5)	92	(77–100)	(12/13)
American Indian	39	100	(93–100)	(8/8)	94	(86–100)	(29/31)
Alaskan Native	7	100	(86–100)	(2/2)	100	(91–100)	(5/5)
All other races	36	100	(92–100)	(6/6)	90	(79–100)	(27/30)

CI, confidence interval.

arenas that currently does not exist. This study does not proclaim to have established *the* FAS phenotypic case definition. The case definition must be reached by consensus across clinical and research teams. This study simply presents a methodologic approach that could be used to derive a phenotypic case definition.

ACKNOWLEDGMENTS

We thank Wendy Mouradian, M.D., and Robert M. Fineman, M.D., Ph.D., for their clinical support at the University of Washington FAS Clinic, and Shannon Greenleaf, B.A., for her timely development of the database.

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A case definition and photographic screening tool for the facial phenotype of fetal alcohol syndrome.

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Objectives: **The purpose of this study was to demonstrate that a quantitative, multivariate case definition of the fetal alcohol syndrome (FAS)3 facial phenotype could be derived from photographs of individuals with FAS and to demonstrate how this case definition and photographic approach could be used to develop efficient, accurate and precise screening tools, diagnostic aids and possibly surveillance tools.**

Study Design**: Frontal facial photographs of 42 subjects (0 to 27 years of age) with FAS were matched to 84 subjects without FAS. The study population was randomly divided in half. Group 1 was used to identify the facial features that best differentiated individuals with and without FAS. Group 2 was used for cross validation.**

Results**: In Group 1, stepwise discriminant analysis identified three facial features (reduced palpebral fissure length / inner canthal distance ratio, smooth philtrum, and thin upper lip) as the cluster of features that differentiated individuals with and without FAS in Groups 1 and 2 with 100% accuracy. Sensitivity and specificity were unaffected by race, gender, and age.**

Conclusions**: The phenotypic case definition derived from photographs accurately distinguished between individuals with and without FAS demonstrating the potential of this approach for developing screening, diagnostic, and surveillance tools. Further evaluation of the validity and generalizability of this methodology will be needed. (J Pediatr 1996; 129:33-41)**

Fetal alcohol syndrome is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. FAS is characterized by cognitive/behavioral dysfunction, a unique cluster of minor facial anomalies, and pre- and/or postnatal growth deficiency[1]. FAS is the leading known cause of mental retardation in the Western World[2] with an estimated incidence of 1 to 3 per 1,000 live births[3]. Individuals with FAS endure lifelong physical, intellectual, cognitive and behavioral disabilities. These disabilities are often compounded by secondary emotional and behavioral disabilities such as low self esteem, depression, school failure, and criminality when the syndrome fails to be diagnosed. These secondary disabilities come at a high cost to the individual, their family, and society and can be reduced by early diagnosis and receipt of appropriate intervention[4,5].

See commentary, p. 3

D-score	Discriminant Score
FAS	Fetal alcohol syndrome

Efforts to prevent FAS and its associated secondary disabilities are currently stymied by the lack of efficient and effective surveillance, screening, and diagnostic tools.

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Development of these tools have, in turn, been stymied by the lack of an effective FAS case definition[6]. An ideal case definition for screening and surveillance of FAS would focus on the minimum cluster of features unique to FAS which are amenable to accurate, precise, and efficient measurement. The FAS facial phenotype is characterized by a cluster of minor facial anomalies which include small palpebral fissures, smooth philtrum, and thin upper lip[1]. Criteria have never been established regarding how small, how smooth, or how thin these features must be nor have criteria been established as to how many of these features must be present.

The goals of this study were to demonstrate (1) that an objective, quantitative, multivariate case definition of the FAS facial phenotype could be derived from facial photographs and (2) that this methodologic approach could be used to develop highly efficient, accurate, and precise screening tools, surveillance tools, and diagnostic aids for FAS.

METHODS

Overview. Frontal facial photographs of 42 subjects with FAS (birth to 27 years of age) were pair matched on age, race and gender to the frontal facial photographs of two randomly selected subjects without FAS (n = 84). The 126 patients were randomly divided into two groups (n = 63 per group) balanced on age, gender, and race. Stepwise discriminant analysis was used to identify the facial feature(s) that best differentiated the subjects with and without FAS in Group 1. The multivariate discriminant equation generated from the discriminant analysis in Group 1 served as both the FAS phenotypic case-definition and the method (or screening tool) by which risk of FAS was assessed among patients in Group 2. Application of the screening tool to Group 2 served as an opportunity to test the tool's validity.

Study Population and Photographic Quality. Photographs of FAS cases and controls were selected from among 1,110 frontal facial images of 740 clinical and research subjects stored in a computerized image database. This study was conducted with the approval of the University of Washington and Children's Hospital and Medical Center Human Subjects Divisions.

Computerized images of subjects with FAS have been collected over the years from syndrome diagnosis textbooks, the medical literature, colleagues, and patients examined by one of the authors at the CDC-sponsored University of Washington FAS Clinic. Each patient with FAS who was selected for this study were examined by clinicians with recognized expertise in the diagnosis of FAS and were felt, by the clinician, to have the facial phenotype of FAS at the time of the photograph. There were no age, race, or gender restrictions placed on selection of FAS cases. Each patient with FAS was matched on gender, race, and age at the time of the photograph (within two years), to two control subjects confirmed not to have a diagnosis of FAS. Control subjects may or may not have had documented prenatal alcohol exposure. The study controls were selected from a pool of 560 subjects which included patients seen at the University of Washington FAS Clinic and subjects who had participated in previous morphometric studies. Each pair of controls were randomly selected from among all controls meeting the matching criteria for each FAS case.

Photographs had to meet the following criteria for inclusion into the study: 1) camera aligned in the Frankfort Horizontal plane with minimal left-to-right rotation (i.e., both planes of rotation were within ± 5 degrees by visual inspection), 2) subject had a relaxed facial expression with eyes fully open and lips gently closed, and 3) image had adequate exposure and focus to allow accurate measurement of facial features.

Computer images and facial measures. All photographs were captured at 640 by 480 pixel resolution on a 256 unit gray scale using OPTIMAS (Optimas Corp., Edmonds, Wash.) image acquisition and enhancement software. The images were saved in tag-image-file (TIF) format. To reduce measurement bias, the FAS case/control status of each photograph was masked by cropping two separate images from each original TIF image: 1) a computer image that included just the eyes and 2) a computer image that included just the philtrum and mouth. All facial measurements were collected from these cropped images.

The facial measures recorded from each subject are listed and defined in Table 1. Emphasis was placed on measuring features previously identified as being specific to FAS[7] and features which could be reliably measured from photographs. Right and left palpebral fissure lengths and inner canthal distance were measured using the distance measurement tool in the OPTIMAS software. The photographs did not contain internal measures of scale, therefore a reduced palpebral fissure length / inner canthal distance ratio was used as a proxy measure for small palpebral fissure length. Direct measures obtained from patients diagnosed with FAS at the University of Washington FAS Clinic have confirmed the presence of short palpebral fissure lengths relative to normal inner canthal distances[7],supporting the validity of the proxy measure. The phenotypic expression of philtrum smoothness and upper lip thinness were recorded on 5-point Likert scales (Fig. 1). Upper lip thinness was also recorded on a continuous scale using an objective measure of shape called circularity (or perimeter^2 / area). The circularity of a circle is 4*Pi (about 12.57) which is theoretically the smallest value that this measure can have. As an object tends towards the shape of a line (or thinness), the circularity tends towards infinity. Philtrum contour was also measured objectively by recording pixel luminosity on a 256 continuous gray scale. With the OPTIMAS software, a line was drawn horizontally across

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the philtrum, centered between the upper lip and subnasion, with a length equal to the distance from the left to right corners of the mouth and a width 20% of the vertical distance between the upper lip and subnasion. The length of the line was divided into 100 units of equal size. Pixel luminosity was averaged over each of the 100 units and plotted to portray the gray scale variation (or shadows and highlights cast by the philtral ridges) across the philtrum (Fig. 2). The darkest luminosity in the philtrum furrow was subtracted from the brightest luminosity at a philtrum ridge to generate a measure of philtrum smoothness. The more deeply furrowed the philtrum, the greater the contrast in the luminosity of the ridge relative to the furrow. Upper lip thinness and philtrum smoothness were recorded on both Likert ordinal scales and objective continuous scales to assess the reliability and utility of each. The Likert scale has the advantage of being technologically simple, meaning the feature can be scored by hand in the event a computer is unavailable. The disadvantage is lower accuracy and precision. In direct contrast, the continuous measures of circularity and luminosity have the advantage of total objectivity, resulting in high accuracy and precision, but require access to appropriate software for derivation.

Discriminant analysis. Stepwise discriminant analysis (maximizing the Wilk lambda) was used to identify the facial feature(s) that best differentiated patients with and without FAS in group 1. Prior probability of FAS was set equal to the prevalence in the study sample (33%). The unstandardized canonical discriminant function coefficients were computed to derive the discriminant equation for calculation of each subject's discriminant score or D-score. The D-score was used to *predict* each subject's diagnostic classification (FAS, not FAS). The D-score distribution for the subjects with and without FAS in group 1 were plotted to identify the D-score cutoff value that resulted in the most accurate diagnostic prediction (i.e., had the highest level of sensitivity and specificity). Sensitivity is the proportion of patients with FAS who are correctly screened as having FAS. Specificity is the proportion of patients without FAS who are correctly screened as *not* having FAS. Sensitivity and specificity were computed by comparing each subject's true clinical diagnosis to their predicted diagnosis derived from the discriminant equation.

For cross validation, the discriminant equation and D-score cutoff value derived from group 1 were applied to group 2. Sensitivity and specificity for group 2 were computed by comparing each subject's true diagnosis with their predicted diagnosis.

RESULTS

The total population of 42 subjects with FAS and 84 controls were successfully balanced on gender, race, and age at the time the photograph was taken (Table II).

Table I. Facial measures recorded from the computerized frontal facial photographs

Facial feature	Description (units of measurement)
Eye region	
Palpebral fissure lengths	Distance between outer and inner canthi of right and left eyes (centimeters of computer monitor screen)
Inner canthal distance	Distance between right and left inner canthi (centimeters of computer monitor screen)
Mouth region	
Philtrum smoothness	Area between upper lip and subnasion, with focus on presence of midline vertical furrow bordered by two vertical ridges (Fig.1)
	5-Point Likert ordinal scale (1 deeply furrowed, 2 somewhat furrowed, 3 mid range, 4 somewhat smooth, 5 very smooth)
	Pixel luminosity: contrast between philtrum's ridges and furrow—the lower the contrast, the smoother the philtrum (0 to 255 continuous gray scale: 0 = white, 255 = black)
Upper lip thinness	Upper lip demarcated by its vermilion border (Fig.1)
	5-Point Likert ordinal scale (1 very thick, 2 somewhat thick, 3 mid-range, 4 somewhat thin, 5 very thin)
	Circularity – the larger the circularity, the thinner the upper lip (perimeter^2/area)

The age distribution of the study population was as follows: birth to two months (n = 1), 3 to 12 months (n = 4), 1 to 5 years (n = 43), 6 to 10 years (n = 46), 11 to 15 years (n = 22), 16 to 20 years (n = 6), 20+ years (n = 4). No two subjects with FAS had an identical pattern of facial features. The variation of phenotypic expression across the 42 subjects with FAS relative to the 84 control subjects is displayed in Fig. 3.

Discriminating facial features and the influence of measurement scale. Stepwise discriminant analysis selected all three facial features (palpebral fissure length / inner canthal distance ratio, philtrum smoothness measured on a Likert scale, and upper lip thinness measured on the continuous scale of circularity) as the cluster of features that best differentiated the patients with and without FAS. When the ordinal and continuous scales used to measure philtrum smoothness and upper lip thinness were interchanged in the discriminant equation, sensitivity and

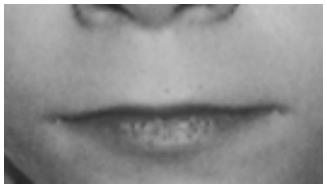
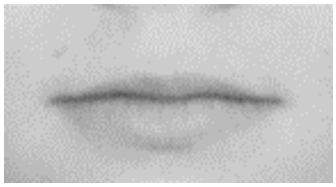
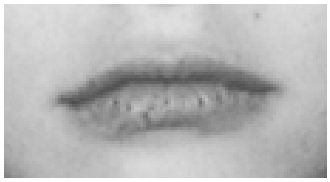
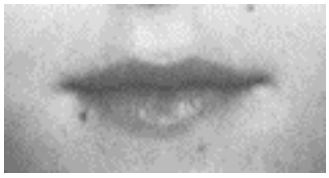
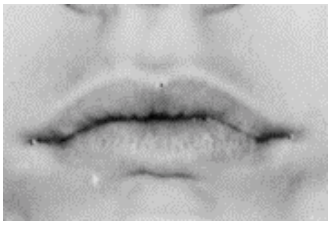
	Philtrum/Upper Lip	Philtrum Likert Score	Upper Lip Likert Score	Philtrum Luminosity	Upper Lip Circularity
A		5	5	0	178.6
B		4	4	2	72.0
C		3	3	4	55.1
D		2	2	7	50.0
E		1	1	15	44.5

Fig. 1. Pictorial examples of the 5-point Likert ordinal scales used to rank upper lip thinness and philtrum smoothness. The corresponding continuous measures of upper lip circularity (perimeter^2/area of vermilion border) and philtrum luminosity (contrast in pixel luminosity between the philtral ridge and furrow with luminosity measured on a 256 unit gray scale) are also presented.

specificity were minimally influenced. The discriminant classification and cross validation results are presented below for each measurement scale.

Philtrum and upper lip measured on a Likert scale. When palpebral fissure length / inner canthal distance ratio, philtrum smoothness measured on a Likert scale, and upper lip thinness measured on a Likert scale were entered into the discriminant equation derived from group 1, a D-score greater than 0.7 differentiated the subjects with and without FAS with 100% sensitivity and specificity.

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Table II. Demographic profile of subjects with and without FAS

Characteristic	Control group (n=84)	FAS group (n=42)
Age (yr)		
Mean (SD)	7.9(4.7)	6.5(5.2)
Minimum-maximum	1.5-26.7	0.0-24.2
Gender		
Girls: n(%)	28(33)	14(33)
Race: n(%)		
White	64(77)	32(77)
Black	4(5)	2(5)
American Indian	10(12)	5(12)
Alaskan Native	2(2)	1(2)
Asian	2(2)	1(2)
Hispanic	2(2)	1(2)
Other syndromes: n(%)		
Williams syndrome	1(1)	0(0)
Dubowitz syndrome	1(1)	0(0)
Aarskog syndrome	1(1)	0(0)
Marfan syndrome	1(1)	0(0)

When this discriminant equation and D-score cutoff value were applied to group 2 for cross validation, subjects from group 2 were also differentiated with 100% sensitivity and specificity.

The discriminant equation (equation 1) derived across all 126 subjects, was as follows: D-score=0.7408-- 5.7337 (palpebral fissure length / inner canthal distance ratio) + 1.1677 (philtrum Likert score) + 0.1587 (upper lip Likert score). A D-score greater than 0.8 was the cutoff value for classifying a subject as having FAS on the basis of screening (sensitivity = 100%, specificity = 100%, overall accuracy = 100%). Discriminant equation 1 explained 100% of the total variance (chi-square value [3, 126] = 224, p = .0000).

Philtrum and upper lip measured on continuous scales. When palpebral fissure length / inner canthal distance ratio, philtrum smoothness measured on the continuous scale of luminosity, and upper lip thinness measured on the continuous scale of circularity were entered into the discriminant equation derived from group 1, a D-score less than -0.5 differentiated the subjects with and without FAS with 95% sensitivity and 100% specificity. When this discriminant equation and D-score cutoff value were applied to group 2 for cross validation, subjects from group 2 were differentiated with 100 % sensitivity and 93 % specificity.

The discriminant equation (equation 2) derived across all 126 subjects was as follows:D-score = -6.4719 + 8.6104 (palpebral fissure length / inner canthal distance ratio) + 0.0767 (philtrum luminosity) - 0.0145 (upper lip circularity). A D-score less than -0.5 = cutoff value for classifying a subject as having FAS on the basis of screening (sensitivity = 99%, specificity = 95%, overall accuracy = 98%).

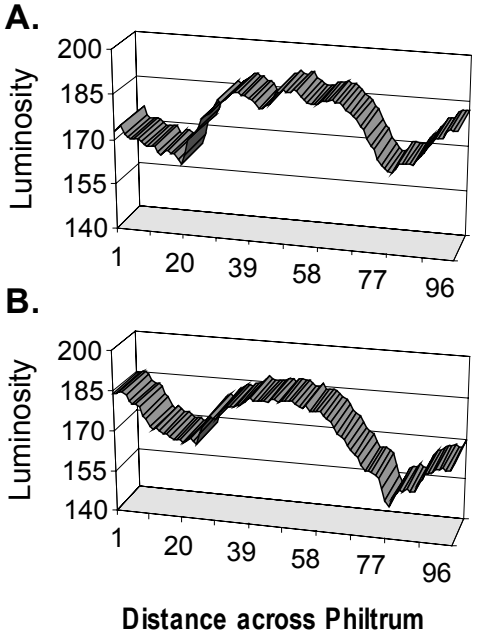

Fig. 2. Plot of pixel luminosity on a 256 unit gray scale along a line drawn horizontally across the philtrum from the left corner of the mouth (x axis = 1) to the right corner of the mouth (x axis = 100). A luminosity of 0 = black and a luminosity of 255 = white. **A**. Example of a deeply furrowed philtrum (Likert scale = 1). **B**. Example of a very smooth philtrum (Likert scale = 5).

Discriminant equation 2 explained 100% of the total variance (chi-square value [3,126] = 130, p = .0000).

Philtrum measured on a Likert scale, upper lip measured on a continuous scale. When palpebral fissure length / inner canthal distance ratio, philtrum smoothness measured on a Likert scale, and upper lip thinness measured on continuous scale of circularity were entered into the discriminant equation derived from group 1, a D-score greater than 0.7 differentiated the subjects with and without FAS with 100% sensitivity and specificity. When this discriminant equation and D-score cutoff value were applied to group 2 for cross validation, subjects from group 2 were also differentiated with 100% sensitivity and specificity.

The discriminant equation (equation 3) derived across all 126 subjects was as follows: D-score =1.1075 - 6.0082 (palpebral fissure length / inner canthal distance ratio)+ 1.1448 (philtrum Likert score) + 0.0066 (upper lip circularity). A D-score greater than 0.7 = cutoff value

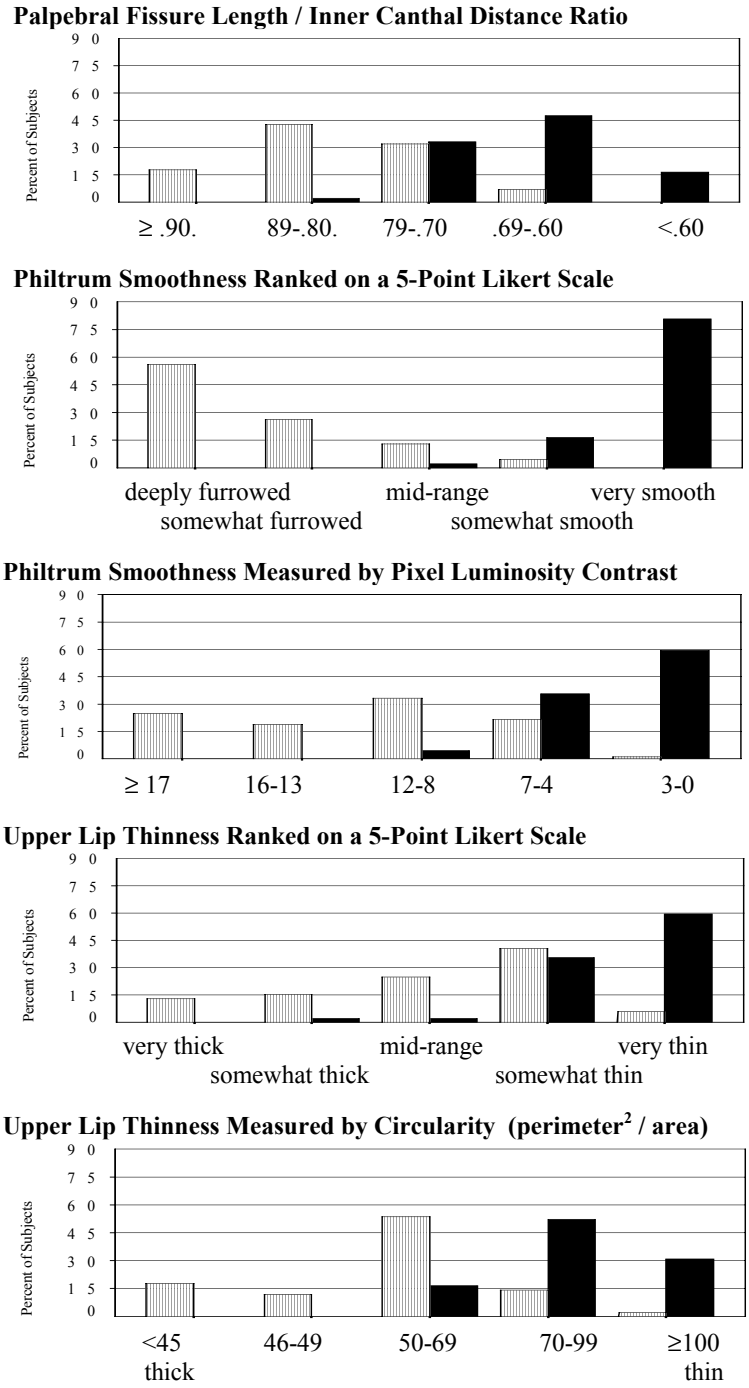

Fig. 3. Variation in expression of facial features among the 42 subjects with (black bars) FAS and 84 subjects without (*gray bars*) FAS. The circularity measure of upper lip thinness reflects the perimeter^2/area of the vermilion border. Philtrum luminosity contrast reflects the contrast in pixel luminosity between the philtrum's ridge and furrow, with luminosity recorded on a 256 unit gray scale.

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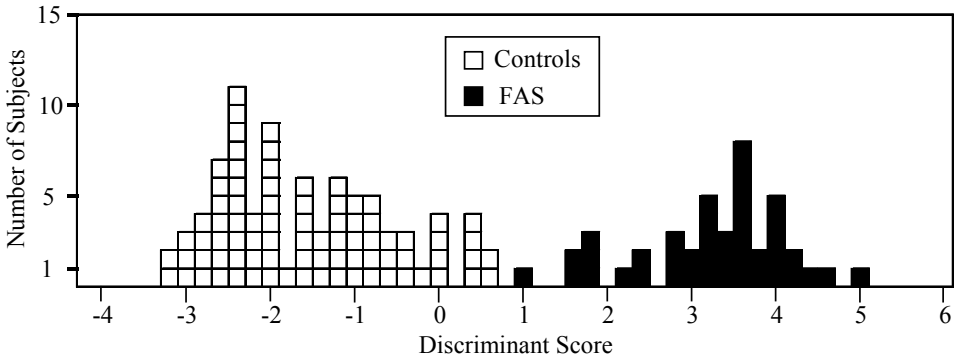

Fig. 4. Distribution of discriminant (*D*) scores among the patients with and without FAS based on the following discriminant equation: D-score = 1.1075 - 6.0082 (palpebral fissure length/inner canthal distance ratio)+ 1.1448 (philtrum Likert score) + 0.0066 (upper lip circularity). (The discriminant equation was derived across all 126 subjects.)

classifying a subject as FAS on the basis of screening (sensitivity = 100%, specificity = 100%, overall accuracy = 100%).

Equation 3 reflects the most objective, sensitive, and specific discriminant function explaining 100% of the total variance (χ^2 [3,126] = 226, p = .0000). The distribution of D-scores for all 126 subjects with and without FAS, derived from equation 3, is presented in Fig. 4.

Sensitivity and specificity across all six discriminant equations were unaffected by race, gender, and age in this study population.

Of the 84 control subjects, four had other syndrome diagnoses: Marfan syndrome, Williams syndrome, Dubowitz syndrome and Aarskog syndrome. All discriminant equations correctly screened the four subjects as not having FAS.

DISCUSSION

This study has demonstrated that a phenotypic case definition of FAS can be derived from frontal facial photographs of individuals with FAS. It has also illustrated how this case-definition and methodologic approach can be used to develop an accurate and precise screening tool and diagnostic aid. The discriminating cluster of facial features identified from the photographs are identical to the facial features identified by direct facial measurement in a previous study[7], thus supporting the validity of this photographic approach. Sensitivity and specificity were unaltered by race, gender, and age in both this and the previous study populations[7], supporting the potential generalizability of this methodology. Further studies, however, will be necessary to more definitively evaluate phenotypic variation that may occur across races.

It was particularly encouraging that the computer was able to identify a common phenotypic pattern in patients whom FAS was diagnosed by more than one clinician, not only illustrating that a phenotypic consensus can be reached, but also illustrating a method by which to establish such a consensus. This is not to say that phenotypic classification does not vary across the clinical and research communities. One need only review the literature[8] and published photographs to see how broadly the original[1, 10] and revised[10] descriptions of the FAS facial phenotype are interpreted, resulting in misclassification of research subjects and misdiagnosis of clinical patients. It is not that clinicians and researchers cannot consistently identify the facial phenotype; they simply do not have sufficiently specific guidelines for achieving such consistency.

To further test the ability of the function to differentiate between FAS and other syndromes with similar facial phenotypes, facial measures were obtained from the photographs of 10 additional control subjects published in syndrome diagnostic textbooks with the following syndromes: fetal hydantoin syndrome, Dubowitz syndrome, Noonan syndrome, Turner syndrome, Bloom syndrome, Aarskog syndrome and Opitz syndrome. Ages ranged from 1 to 20 years, with a distribution comparable to the 126 subjects with and without FAS. All but the individual with fetal hydantoin syndrome were classified correctly as not having the facial phenotype of FAS. This suggests that this screening tool will effectively separate the dysmorphic features of FAS from normal and also from many, but not necessarily all, other syndromes.

A key factor in the success of this study was the quality of the photographic images. It is important to note that all photographs were taken by nonprofessional photographers using handheld cameras. Obtaining a quality photograph does not require sophisticated equipment or expertise. One need only focus on three elements: proper alignment[11], proper exposure, and a relaxed facial expression, all of which can be easily attained by shooting a test roll of film with a properly aligned photograph in hand as a guide.

Table III. Contrasts in facial features and discriminant scores between the study groups with and without FAS.

Predictor and Outcome Variables	Control group (n = 84)	FAS group (n = 42)	Test statistic	p
Right palpebral fissure length / inner canthal distance ratio				
Mean (SD)	0.83(0.09)	0.67(0.07)	t = 10.1	.000
Minimum-maximum.	0.65-1.12	0.60- 0.88		
Philtrum, 5-point Likert Scale, n (%)				
Deeply furrowed	47(56.0)	0(0)	U = 23.5*	.0000
Somewhat furrowed	22(26.2)	0(0)		
Mid-range	11(13.0)	1(2.3)		
Somewhat smooth	4(4.8)	7(16.7)		
Very smooth	0(0)	34(81.0)		
Philtrum luminosity*				
Mean (SD)	14.2(9.0)	3.4(2.5)	t = 10.3	.000
Minimum-maximum	3-45	0-10		
Upper lip, 5-point Likert Scale, n (%)				
Very thick	11(13.0)	0(0)	U = 509*	.0000
Somewhat thick	13(15.5)	1(2.4)		
Mid-range	21(25.0)	1(2.4)		
Somewhat thin	34(40.5)	15(35.7)		
Very thin	5(6.0)	25(59.5)		
Upper Lip, circularity†				
Mean (SD)	57.5(14.8)	101.5(49.3)	t = -5.7	.000
Minimum-maximum	28.2-115.8	50.6-343.2		
Discriminant score, equation 1‡				
Mean (SD)	-1.6(1.1)	3.2(0.8)	t = -27.9	.000
Minimum-maximum	-3.9-0.7	1.1-4.4		
Discriminant score, equation 2§				
Mean (SD)	-1.6(1.0)	3.2(0.9)	t = -25.6	.000
Minimum-maximum	-4.1-0.7	1.1-5.1		
Discriminant score, equation 3□				
Mean (SD)	1.0(1.0)	-1.9(1.0)	t = 15.0	.000
Minimum-maximum	-1.6-4.4	-5.7- -0.5		

* Mann-Whitney υ Test
* Contrast in pixel luminosity between philtral ridge and furrow measured on a 256 unit gray scale.
† Perimeter^2 / area.
‡ Based on Discriminant Equation 1: D = 0.7408 - 5.7337 (palpebral fissure length/inner canthal distance ratio) + 1.1677 (philtrum Likert score) + 0.1587 (upper lip Likert score) derived across all 126 subjects.
§ Based on Discriminant Equation 2: D = -6.4719 + 8.6104 (palpebral fissure length/inner canthal distance ratio) + 0.0767 (philtrum luminosity) - 0.0145 (upper lip circularity) derived across all 126 subjects.
□ Based on Discriminant Equation 3: D = 1.1075 - 6.0082 (palpebral fissure length/inner canthal distance ratio) + 1.1448 (philtrum Likert score) + 0.0066 (upper lip circularity) derived across all 126 subjects.

Recording facial measurements indirectly from a photograph rather than directly from the face has several advantages. By capturing a photographic or computer image, all three key facial features can be recorded on objective, continuous scales with the aid of computer software. This approach maximizes measurement accuracy and precision. If computer-derived continuous measures can be developed which validly capture the information obtained by the Likert scales, the process of phenotypic classification could be computer automated. The results of this study support the feasibility of such an endeavor. The continuous measure of circularity used to measure lip thinness was highly correlated with the Likert ranking (Spearman rank correlation coefficient 0.84: p = 0.000) and performed with equal sensitivity and specificity (100%). The continuous measure of luminosity used to measure philtrum smoothness was also highly correlated with the Likert ranking (Spearman rank correlation coefficient 0.74: p = 0.000). Although sensitivity and specificity dropped by 1% and 5%, respectively, modification of the luminosity measure could help regain the discriminating power. The increased accuracy, precision, and efficiency which could be achieved with this computerized photographic approach are all key to developing effective surveillance tools, screening tools, and diagnostic aids.

No two individuals with FAS have identical facial features; all, however, present with the overall gestalt. To define the gestalt, one must take a multivariate approach, not a univariate check list approach as illustrated in Fig. 3.

The discriminant analysis used in this study accomplished this by identifying both the minimum number of features and the magnitude of expression of each feature that most accurately differentiated individuals with and without the facial gestalt. The discriminate analysis identified short palpebral fissures, smooth philtrum, and thin upper lip as the minimum cluster of features needed to define the phenotype and differentiate individuals with highest accuracy. Further studies to confirm the validity and generalizability of these study results will be necessary. In the discriminant equation, the three facial features serve as the predictor variables, each with a beta coefficient reflecting their level of contribution to the overall gestalt appearance. The equation computes a discriminant score which, in essence, is a proxy measure of the gestalt appearance recorded on a continuous scale. To use this equation, one would measure the three facial features from a photograph, insert the values into the equation, compute the discriminant score, and classify the phenotype based on whether the individual's discriminant score fell above or below the cutoff value. This equation not only provides a method by which to differentiate individuals with and without the facial phenotype of FAS but also provides a standardized objective language in which clinical researchers can describe the magnitude of expression of the phenotype in their study populations for comparative purposes.

Surveillance generally uses methods distinguished by their practicality, uniformity, and frequently their rapidity, rather than by complete accuracy[12]. To date, effective methods for FAS surveillance do not exist[13]. Passive surveillance such as hospital-based birth defects registries[14] examine only the medical record, not the patient, and focus on an age group when FAS is known to be misdiagnosed and underreported[15]. Passive surveillance has resulted in marked underestimation of FAS prevalence. In contrast, active surveillance relies on direct collection of data from patients and, although more costly, results in more valid and reliable data and results in estimated rates of FAS that are an order of magnitude higher than those estimated from passive surveillance[13]. The results of this study demonstrate that computerized analysis of facial photographs has the potential for serving as a highly efficient, reproducible, and potentially highly accurate active surveillance tool. Photographic analysis has the following advantages: 1) photographic images are inexpensive, 2) they do not require professional expertise or sophisticated equipment to collect; 3) they can be stored and analyzed with complete anonymity by cropping the images; 4) data can be transferred over the Internet for centralized analysis maximizing consistency of interpretation; 5) use of a highly accurate and objective case definition would result in highly reproducible results over time which is paramount to tracking trends; and 6) population-based surveillance of more representative segments of the population could be achieved because a broad age range can be accurately assessed and surveillance need not be restricted to hospital or research institutions because of the ease with which data can be collected.

Primary prevention of secondary disabilities associated with FAS will require accurate and reliable screening tools and diagnostic aids. Unlike surveillance, screening and diagnosis target individuals for the purpose of early identification and intervention. An ideal screening tool is highly sensitive, specific, accurate, precise, reproducible and valid. This tool has demonstrated all of these qualities in this study population.

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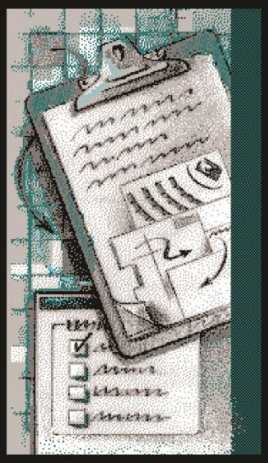

FAS Facial Photographic Analysis Software

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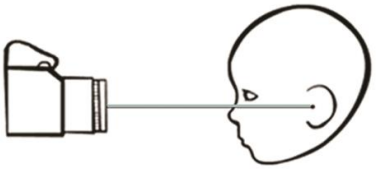
Fetal Alcohol Syndrome Diagnostic & Prevention Network
University of Washington, Seattle, WA

ww.fasdpn.org
Version 2.1.0



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Watch for Updates on the FAS DPN Website

fasdpn.org

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About FAS Facial Photographic Analysis Software

FAS Facial Photographic Analysis Software [Version 2.1.0]

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PART I. INTRODUCTION

What is Fetal alcohol syndrome (FAS)?

Fetal alcohol syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. The syndrome has been broadly characterized by pre- and/or postnatal growth deficiency, a characteristic set of minor facial anomalies, central nervous system (CNS) abnormalities (Jones and Smith, 1973; Clarren and Smith, 1978; Smith, 1979; Rosett, 1980; Sokol and Clarren, 1989; Stratton *et al*., 1996). Although these previous publications do provide guidance, they are not sufficiently specific to assure diagnostic accuracy and precision. In 1997, a new more rigorous and comprehensive, case-defined method for diagnosing the full spectrum of outcomes in individuals with prenatal alcohol exposure was created called the FASD 4-Digit Diagnostic Code (Astley & Clarren, 1997, 1999, 2000; Astley et al., 1999, Astley, 2004a). The 4-Digit Code is a validated set of guidelines intended for use by an interdisciplinary team in a FASD diagnostic clinic (Astley, 2011, 2013; Astley et. al. 2009).

The FASD 4-Digit Diagnostic Code

The four digits of the diagnostic code reflect the magnitude of expression of four key diagnostic features of FAS/D in the following order: (1) growth deficiency, (2) the FAS facial phenotype, (3) CNS abnormalities, and (4) gestational alcohol exposure (Fig. 1). The 4-Digit Diagnostic Code is generated by first recording key clinical data on the standardized FASD Diagnostic Evaluation Form and following specific case-definitions to generate each digit.

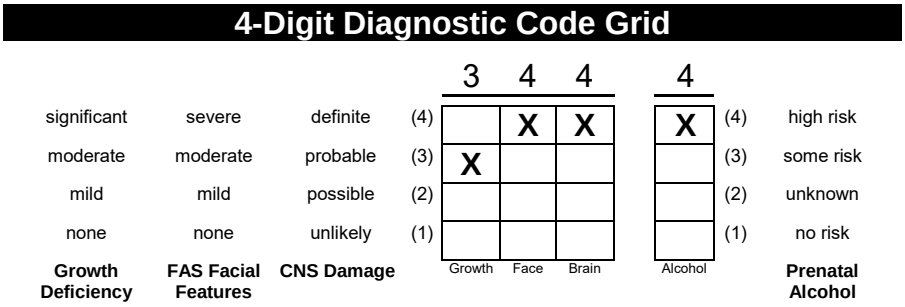


Fig. 1. The magnitude of expression of each feature is ranked independently on a 4-point Likert scale with 1 reflecting complete absence of the FAS feature and 4 reflecting a strong "classic" presence of the FAS feature. Each Likert rank is specifically case-defined. The 4-Digit Diagnostic Code can be used to diagnose individuals of all ages. The 4-Digit Diagnostic Code has been used effectively for diagnosis (Astley & Clarren, 2000), screening (Astley et. al., 2002) and surveillance (Astley, 2003) efforts in the Washington State FAS Diagnostic & Prevention Network of clinics since 1997 (Astley et al., 2014). The 2004 diagnostic guide entitled "*Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code*" the *Lip-Philtrum Guides*, and the *FAS Facial Photographic Analysis Software* can be ordered from the website fasdpn.org.

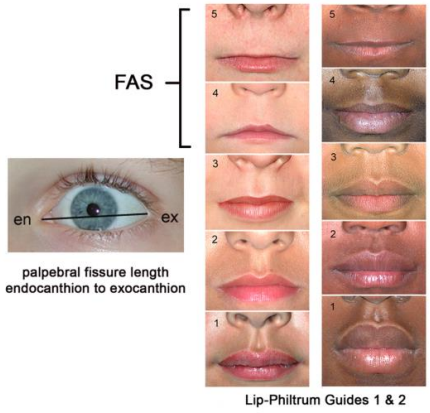
Facial Features of FAS

The most specific feature of FAS is the facial phenotype. The FAS facial phenotype is characterized by the presence of all three of the following minor anomalies at any single point in time:

1. **Palpebral fissure lengths** (PFL) two or more standard deviations below the mean.

2. A **smooth philtrum** defined as a Rank 4 or Rank 5 on the 5-point likert scale depicted on the FAS DPN Lip-Philtrum Guides (Astley & Clarren, 1999, 2000).

3. A **thin upper lip** (thin vermilion border) defined as a Rank 4 or Rank 5 on the 5-point Likert Scale depicted on the FAS DPN Lip-Philtrum Guides (Astley & Clarren, 1999, 2000).



This case-definition for the FAS facial phenotype was derived empirically by Astley and Clarren (1995, 1996), matches the original definition by Smith (1979), and is confirmed to be highly sensitive and specific to FAS and prenatal alcohol exposure (Astley & Clarren 1996, 2001; Astley et al., 2002; 2009; 2013).

Other facial anomalies may be present. The presence of other anomalies should be recorded, but should not be used in lieu of any of the three diagnostic features (small palpebral fissures, smooth philtrum, and thin upper lip) of the FAS facial phenotype.

FAS Facial Analysis Software

This software was developed for use by health care and medical research professionals. Computerized image analysis has been used effectively to measure and rank the magnitude of expression of the FAS facial phenotype on thousands of individuals evaluated in the FAS DPN clinics (Astley & Clarren, 2001; Astley et al., 2002, Astley, 2010. 2013). This software was developed to provide healthcare professionals with a user-friendly, inexpensive, objective method for analyzing facial photographs obtained in a clinical or research setting. Please read the License Agreement for further details.

PART II. GETTING STARTED

Professional qualifications for use of this software

This software is intended for use by healthcare and research professionals.

Computer System

This software is a Microsoft WINDOWS application. Please go to fasdpn.org for computer system specifications.

To Install the Facial Software, Version 2.0.0 (2012) or Version 2.1.0 (2016)

Please go to the fasdpn.org website for the most current installation instructions.

To Upgrade from Version 1.0.0 (2003) to Version 2.0.0 (2012) or Version 2.1.0 (2016)

Please go to the fasdpn.org website for the upgrade instructions.

Version 2.0.0 provides the following additional features:

1. Two additional PFL normal growth charts are included: Canadian and Scandinavian. These new charts are considered more accurate (Astley, 2011a) growth charts for Caucasian PFLs than the Hall (1989) PFL growth charts. See more details posted on the fasdpn.org website.

2. Version 1 required all photo analysis data be stored in a single database file that could only be named **data.fas.** This file was permanently positioned in the FAS software's data directory in the following path (**C:\Program Files\FAS\Data\data.fas**). Version 2 allows the User to assign any name to the database file (e.g., **data2012.fas**) and place it anywhere on their hard drive or server. By default the Version 2 database file is named **data2012.fas** and is placed in the following path (**C:\FAS\Data\data2012.fas**). The User can create multiple database files. They can browse to locate and select which database file they want their photo analysis data to be stored in.

Version 2.1.0 includes the new Lip-Philtrum Guides with frontal and ¾ view images.

A User can upgrade to Version 2.0.0 or 2.1.0 without losing the photo analysis data they have accumulated to date using Version 1.0.

Help

A copy of the License Agreement and a copy of this Instruction Manual can be found by clicking on the Help button in the top menu bar when the software is open. Please use your IT support personnel.

Fundamentals Regarding Version 2

1. The software installation program loads the software in a FAS folder off the C: drive **C:\FAS**

2. The data you generate from analyzing photographs is stored in a Microsoft Access database that comes with the software. This is why the software requires you to have Microsoft Office/Access installed.

3. When you install the software, the Access database is assigned the default name **data2012.fas** and is placed in the following path: **C:\FAS\Data\data2012.fas**

4. After you install the software, you can assign any name to this Access database as long as it ends in **.fas**. You can also store the Access database anywhere on your computer. And you can create more than one Access database to store your photo analysis data.

5. Your photo images are NOT stored in the software's Access database. Your photo images are stored wherever you decide to store them on your computer. When you open a photo into the software for analysis, the software stores the current location (or path) of the photo on your hard drive in the Access database. This allows the software to locate the photo if you choose to evaluate it again. If you move the photo on your hard drive after you have analyzed the photo, the software will not know where to find the photo. The Access database only stores the original location (path) of the photo. Keep this in mind as you organize your photos for analysis.

6. The facial software contains formulas to calculate palpebral fissure length (PFL) and inner canthal distance (ICD) z-scores. These formulas are generated from published growth charts. These formulas are stored in the same Access database as your photo analysis data. If you are installing Version 2 of the software, these formulas come with the default Access database (**data2012.fas**). If you have Access databases created with version 1.0, some of these formulas (Canadian and Scandinavian formulas) will be missing. This will not pose a problem. There are directions below for how to import these new formulas into your version 1.0 databases.

7. You can load this software on as many computers as you like.

8. We cannot provide software support. We recommend you involve your IT support personnel when installing this software.

To Open the Software

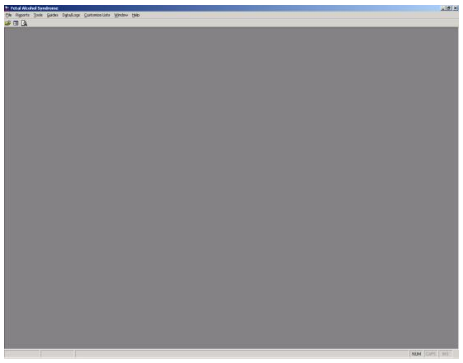


Fig. 2. This blank screen will appear when you open the software.

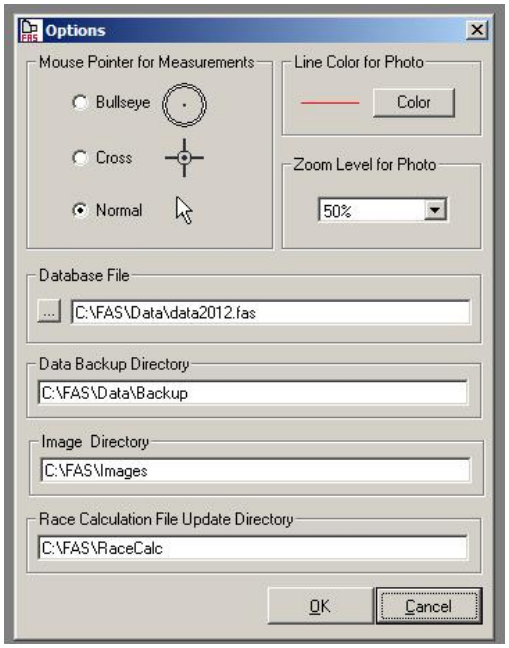


Fig. 3. The Options window allows you to select the directory where you want your backup files to be stored. It also allows you to designate which folder to go to first to look for new images to analyze.

1. Left mouse click on the Windows start button in the lower left corner of your monitor. Left mouse click on "Launch FAS.exe".

2. The software will open to the following blank screen (Fig. 2).

3. If you loaded Version 2.0 or 2.1 for the first time, the software will open, pointing to the default **data2012.fas database,** where your photo analysis data will be stored. This blank database comes with one "practice case: John Doe" permanently stored in it (for training purposes). When you start analyzing photos, your data will also be stored in this database.

4. If you want to store your data in a different database (perhaps a previous database with photo analysis data already in it that you created using Version 1.0), do the following:

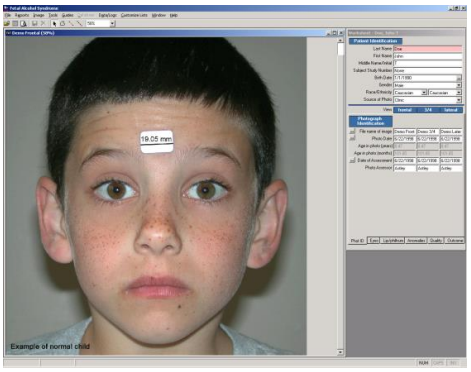
   a) Left mouse click Tools in the menu at the top (Fig. 2). Left mouse click on Options from the drop-down menu to open the Options screen (Fig. 3).

   b) Left mouse click on the browser button under "Database File" (Fig. 3). Navigate to the **.fas** database you want to store your photo analysis data in.

   c) Click OK. Restart the software.

   d) IMPORTANT: If you selected a **.fas** database created from Version 1.0, the new Canadian and Scandinavian PFL growth charts will be missing. See "**Importing New Racial Calculations for PFL Z-scores**" below.

To Open the "John Doe" Demonstration Case



John Doe Demonstration/Practice Case
John Doe has normal facial features.

Follow the instructions below to open the existing demonstration case called "John Doe".

This fictitious demonstration case provides an example of a completed analysis. It also serves as a Practice Case. Instructions for using the Practice Case are presented later in this Instruction Manual.

1. To open Select File/Open/Existing Subject File from the top menu bar.

2. Double-click on the file named John Doe.

3. Click on the OK button.

PART III. TAKING THE FACIAL PHOTOGRAPHS

How to take the 3 standardized facial photographs

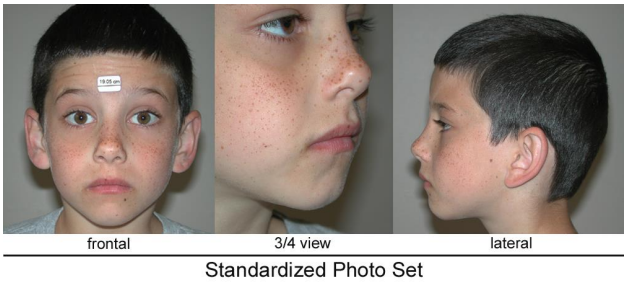


Fig 4. Standardized Photo Set Guide. Example of a normally developed child.

Internal Measure of Scale: An internal measure of scale (adhesive paper sticker) is placed on the patient's forehead between their eyebrows (Fig. 4). It should not be placed high on the forehead or off center to the right or left. A small, adhesive paper sticker 1/2 inch to 3/4 inch in size serves well and can be purchased from an office supply store. Do not use "homemade' stickers. Use store-bought stickers that are machine cut for accuracy. Make sure the sticker is firmly attached (not curled up along the edges). Print the size of the sticker on the sticker.

Frontal, ¾ and Lateral Pictures: A frontal, a ¾ view, and a lateral photograph of the patient's face are obtained using a digital camera (Fig. 4). The ¾ view is taken to facilitate ranking philtrum smoothness by purposely driving a flash of light across the philtrum to see if a shadow is cast. Stand approximately 3 feet from the patient and zoom in with the camera lens so that the patient's head fills the entire frame. This provides the highest resolution image. Be careful not to distort the photo by holding the camera too close to the patient's face (see our website fasdpn.org for more details).

Facial Expression: The facial expression should be relaxed with no smile, lips gently closed, eyes wide open and no eyeglasses. A smile will make the lip appear thinner and the philtrum appear smoother than they truly are (Fig. 5).

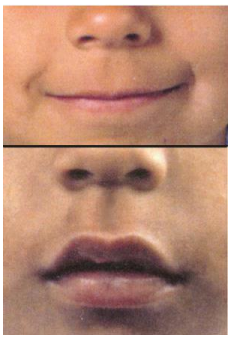


Fig. 5. This is the same child with and without a smile. When the child smiles, her lip appears thinner and her philtrum appears smoother than it truly is. Rankings based on the top photo would be inaccurate.

Rotation: The lens of the camera should be placed in-line with the patient's *Frankfort Horizontal Plane* as illustrated in Fig. 6A. To determine if the camera is in the patient's Frankfort Horizontal Plane when viewing the face through the camera, an imaginary line drawn between the upper border of the left tragus and right tragus should fall across the left and right lower bony orbital rims (Fig. 6B). There should also be no left-to-right rotation of the image; both ears should be equally visible in the frontal photo.

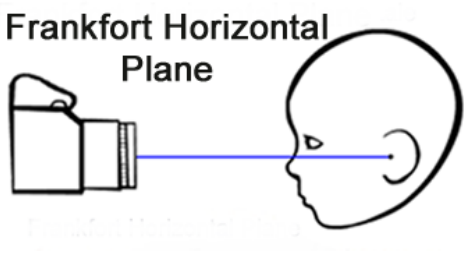


Fig. 6A. The center of the camera lens is placed in the patient's Frankfort Horizontal Plane (a line drawn from the external auditory canal through the lower border of the bony orbital rim (orbitale)).

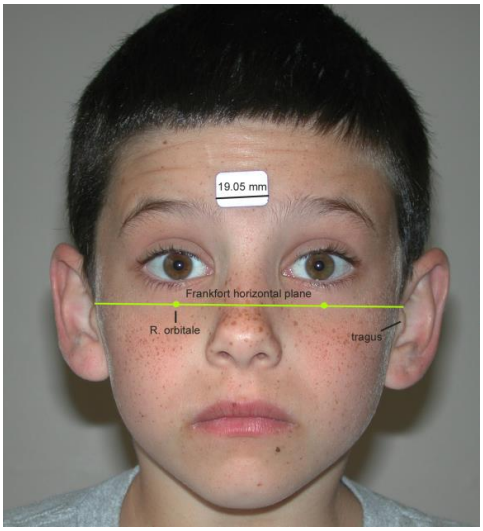


Fig. 6B. When viewing the patient through the camera, the camera is in the patient's Frankfort Horizontal Plane if a line drawn between the left and right auditory canals (or the upper border of the right tragus and left tragus) falls along the right and left orbitale landmarks.

Impact of Rotation on Measurement of Features *Upward –Rotation (head tipped back) w*ill make the upper lip appear thicker than it truly is. All other features will be unaffected. *Downward-Rotation*: will make the upper lip appear thinner than it truly is. All other features will be unaffected. *Right or Left Rotation* will cause the circularity measure for lip thinness to be smaller (thicker) than it truly is because the length of the lip will be foreshortened. The mean PFL and inner canthal distance will remain accurate even with marked left or right rotation as long as the endocanthion and exocanthion landmarks are clearly discernable. The reason mean PFL and inner canthal distance are largely unaffected by right-left rotation is because the internal measure of scale is also rotating by an equal degree.

Properly aligned facial photographs are obtained in the FAS DPN clinics with a hand-held camera and seated patient. Stereotaxic equipment and tripods are not necessary. Take multiple photos if necessary. Sometimes one photo will provide a good measure of the eyes while a second photo will provide a good measure of the lips.

Additional Training / Instructional Resources: More detailed pictorial and animated instruction for how to take standardized facial photographs can be obtained from the FAS DPN website and the research publications by Astley (2011a, 2015) posted on the website.

Camera / Image Resolution Specifications

Digital Camera

The recommended minimum specifications for a digital camera are:

- 3 Mega Pixel resolution or greater
- Flash
- Zoom feature that allows you to fill the camera frame with the facial image.

Image Resolution

In general, an ideal facial image has at least 1000 data points (or pixels) across the width of the face when the image is viewed at its original magnification (or 100% zoom).

Image Formats

This software imports the following image formats

- jpeg (.jpg)
- tiff (.tif)
- bitmap (.bmp)

PART IV. USING THE MEASUREMENT TOOLS, PICTORIAL GUIDES AND SCORING TABLES

Tools and Guides to Measure Facial Features

- Several tools and pictorial guides are provided to help you measure the facial features.
- Select the tools and guides from the TOOLS and GUIDES drop-down menus.
- An image must be open and 'active' before a TOOL can be selected. To activate a photo, click your mouse anywhere on the open photo and the top border of the photo will turn blue.
- Each TOOL and GUIDE is described below.

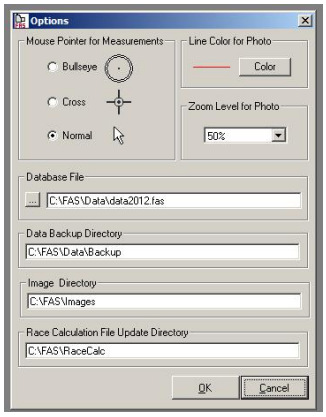
TOOLS include:

- Pointer for pointing to objects.
- Circularity Tool for outlining upper lip thinness.
- Single Distance Tool for measuring the size of the internal measure of scale (paper sticker).
- 3-Distances Tool for measuring the left and right palpebral fissure lengths and the inner canthal distance.
- Tool Options to select style of pointer, line color, etc.

GUIDES include:

- Picture Guides
  1. 2 Lip-Philtrum Guides (Caucasian and Black).
  2. FAS Face/Other Anomalies Guide provides a pictorial example of the FAS facial features and other commonly seen minor facial anomalies.
  3. Rotation Guides (Up/Down, Left, Right) document different degrees of rotation in frontal images.
  4. Landmark/Rotation Guide identifying key facial landmarks and proper image rotation.
  5. Standardized Photo Set Guide providing an example of the frontal, ¾ and lateral photos.
- Table Guide for deriving the ABC-Score for the face.
- Circularity Practice Guide for practicing outline upper lips to compute circularity.

Tool Options Guide



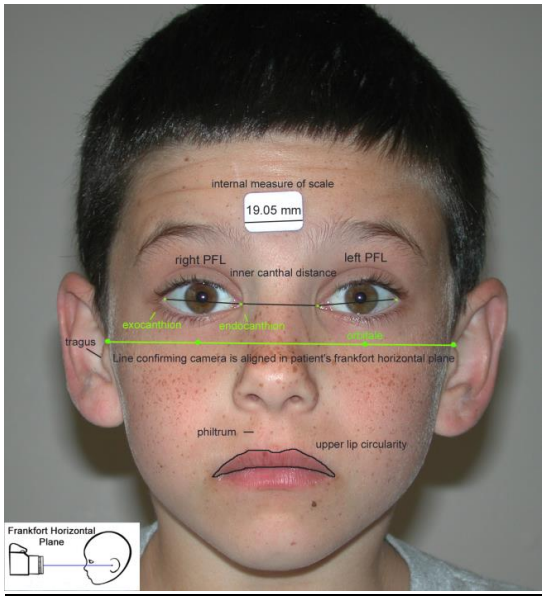
To Use: Select from the Guides drop-down menu from the top menu bar.

The User can select the following options:

- Mouse Pointer style for the Circularity, Single Distance and 3-Distance Tools.
- Line color.
- Default zoom level for the Photo.
- Database File that is currently active.
- Directory where backups will be stored.
- Directory where software will first go to when asked to open a new photo.
- Directory for PFL race formulas.

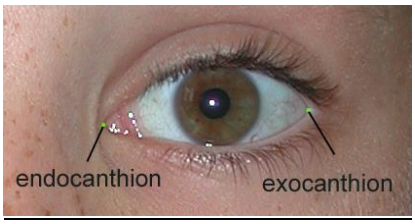
Identifying Key Facial Features

The Landmark/Rotation Guide



To view: Select from the Guides drop-down menu on the top menu bar.

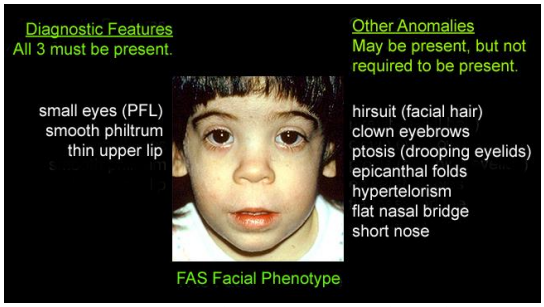
This Guide identifies key facial features (palpebral fissure length (PFL), philtrum, upper lip) and landmarks (endocanthion, exocanthion, orbitale, and tragus) used to measure the FAS facial phenotype. The child pictured has a normal facial phenotype. The Guide also provides a pictorial example of the Frankfort Horizontal Plane used to align the camera with the face. More detailed information about image rotation can be found elsewhere in this Instruction Guide.



Palpebral Fissure Length (PFL)

The palpebral fissure length (PFL) is defined as the distance from the endocanthion landmark to the exocanthion landmark.

The FAS Face and Other Anomalies Guide



Pictorial examples of Diagnostic FAS facial features and other facial anomalies

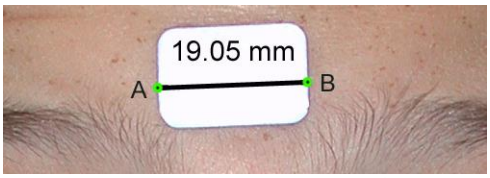
To view: Select from the Guides drop-down menu on the top menu bar.

This young girl presents with the three facial features (listed on the left) that are diagnostic of the FAS facial phenotype. She also presents with other minor facial anomalies (listed on the right) that may or may not be present in an individual exposed to prenatal alcohol exposure. If other anomalies are present, they should be documented, but they are not used to diagnose the FAS facial phenotype.

Measuring the Internal Measure of Scale

The Single-Distance Tool

Single-Distance Tool Icon



Measuring the horizontal length of the internal measure of scale (or paper sticker).

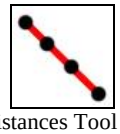
To use: Click the left mouse button on the image then click on the Single-Distance icon or select the tool from the TOOLS drop-down menu on the top menu bar.

This Tool measures the distance between two points. For example, to measure the length of the sticker on the forehead, click on the frontal photo, select the tool and highlight the "Length of Scale in Photo" cell in the Worksheet by clicking in it (the cell will turn pink). Now click and release the left mouse button on point A and click and release the left mouse button on point B. A straight line will be drawn on the photo as an overlay. The sticker length, in units of pixels, will automatically fill into the Worksheet cell.

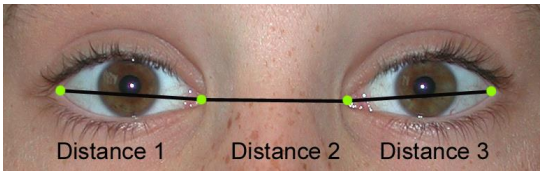
When measuring the internal measure of scale, its horizontal length should be measured, not it's vertical height.

Measuring PFLs and Inner Canthal Distance

The 3-Distances Tool



3-Distances Tool Icon



With the 3-Distances Tool, you can measure these 3 distances (the subject's Right PFL, Inner Canthal Distance and Left PFL) with the following 4 mouse-clicks on the subject's R. exocanthion, R. endocanthion, L. endocanthion and L. exocanthion.

To use: Click the left mouse button on the image, then click on the 3-Distances icon or select the tool from the TOOLS drop-down menu from the top menu bar.

For expediency and accuracy, this Tool measures three distances (R. PFL, Inner Canthal Distance and L. PFL) with just 4 mouse clicks. When the tool is selected, the Worksheet cell for R. PFL is automatically highlighted. Click and release the left mouse button on the patient's R. exocanthion, R. endocanthion, L endocanthion and L exocanthion, in that order. The length in units of pixels for each feature will be automatically displayed in the proper cells on the Worksheet. The true length in mm and z-score of each feature will also be automatically computed if the following cells are filled in: birth date, photo date, normal chart race, gender, real scale length and length of scale in photo.

Measuring Lip Thinness

The Circularity Tool

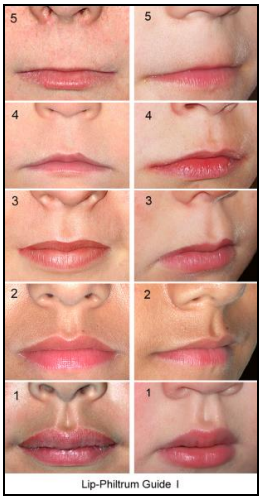
Circularity Icon

An example of the upper lip outlined to compute circularity. This is the most accurate method for measuring upper lip thinness.

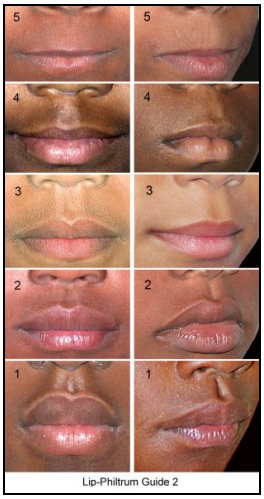
To use: Click the left mouse button on the image, then click on the Circularity Icon or select from the TOOLS drop-down menu from the top menu bar.

This Tool measures the circularity (or thinness) of the upper lip in the frontal photo. Circularity = perimeter^2 /area. The thinner the upper lip, the greater the circularity. When the tool is activated, the user outlines the upper lip while holding the left mouse button down. The left mouse button is released when the outline is complete. Circularity is automatically computed, ranked and inserted into the proper cell of the worksheet. Circularity is a more accurate and objective method for computing lip thinness than simply selecting the picture on the Lip-Philtrum Guide below that best matches the lip in the patient's facial photograph.

The Lip-Philtrum Guides



Guide 1



Guide 2

Lip Rank	Lip Circularity	
	Pictured	Range
5	178	≥ 131.5
4	85	75.5 to 131.4
3	65	57.5 to 75.4
2	50	42.5 to 57.4
1	35	≤ 42.5

Table on backside of Lip-Philtrum Guide 1.

Lip Rank	Lip Circularity	
	Pictured	Range
5	80	≥ 62.1
4	57	52.1 to 62.0
3	39	30.1 to 52.0
2	29	27.5 to 30.0
1	25	≤ 27.5

Table of backside of Lip-Philtrum Guide 2.

To use: Two Guides are available. Guide 1 is used for Caucasians and all other races with lips similar to Caucasians. Guide 2 is used for Blacks and all other races with thicker lips like Blacks. Select a Guide from the GUIDES drop-down menu from the top menu bar. When displayed, place the mouse cursor on the guide and hold the left button down to move the Guide over the surface of the facial photograph.

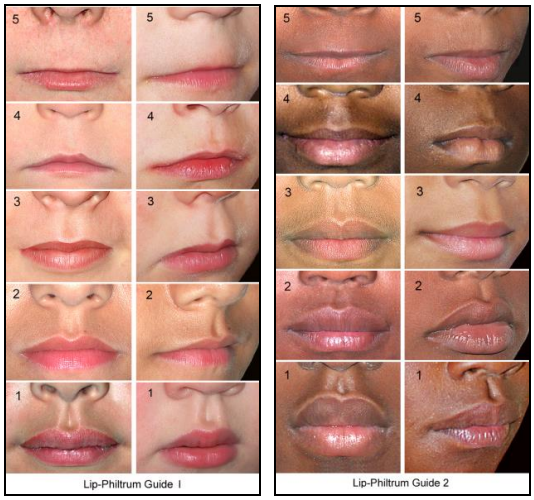
These guides serve as pictorial 5-point Likert Scales for visually ranking upper lip thinness. The user selects the lip rank that best matches the lip thickness in the patient's facial photograph. The Rank of each lip is printed to the left of the each lip photo. The circularity of each lip pictured is printed in a Table on the backside of the Lip-Philtrum Guides. These Tables are reproduced here.

The range of circularity for each Rank is printed in a Lip Circularity Table on the backside of the Lip-Philtrum Guides. Note the ranges differ by race.

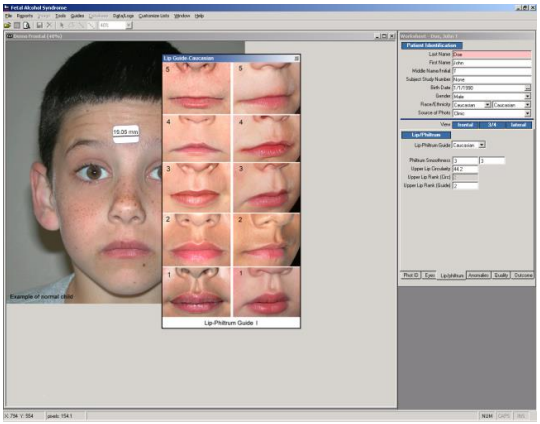
The most accurate measure of lip thinness is obtained using the circularity tool.

Measuring Philtrum Smoothness

The Lip-Philtrum Guides



Guides for ranking
lip thinness and philtrum smoothness.



The Lip-Philtrum Guides can be opened and moved around across the top of the facial image. If the Guide happens to disappear behind the facial image on the computer screen, simply click on "Window" in the top Menu bar and click on the name of the Guide to bring it back in view.

To use: Select from the GUIDES drop-down menu from the top menu bar. When displayed, place the mouse cursor on the guide and hold the left button down to move the Guide over the surface of the facial photograph.

The guides provide a pictorial 5-point Likert Scale for visually ranking philtrum smoothness. The user selects the philtrum that best matches the philtrum in the patient's facial photograph. The rank of the philtrum is printed on the left.

Note that there are two Lip-Philtrum Guides (1 and 2). The philtrum ranks are identical between the two Guides. In other words, the Rank 3 philtrum pictured in Guide 1 is the same depth as the Rank 3 philtrum pictured in Guide 2.

A Rank 5 philtrum is completely smooth. A Rank 4 philtrum is a barely visible indentation that typically must be viewed at an angle to detect. Go to our fasdpn.org website for additional photo examples of Rank 4 and 5 philtrums. A Rank 3 philtrum is the population mean. A Rank 1 philtrum is extremely deep with very prominent philtral ridges. A Rank 1 philtrum will be almost as rare in the population as a Rank 5 philtrum.

Lip thinness and philtrum smoothness are measured independently of one another. In other words, an individual can have a Rank 5 upper lip with a Rank 1 philtrum.

Guide for Scoring the FAS Facial Phenotype

The following Tables are used to derive the facial ABC-Score and the facial 4-Digit Code Rank (Astley, 2004; Astley & Clarren, 2000). These Tables serve as the case-definitions used to describe the full continuum of expression of the FAS facial features.

The user can view these tables by going to the Guides drop-down menu in the top menu bar. The user does not need to refer to these Tables to score the facial phenotype. The software automatically generates an ABC-Score and 4-Digit Diagnostic Code rank for the face when the user measures the palpebral fissure lengths, philtrum smoothness and upper lip thinness. These scores are presented at the end of the Worksheet under the OUTCOME tab.

Table 1A. Deriving the ABC-Score for the Face

The first step in deriving the 4-Digit Code rank for the facial phenotype is to derive the facial ABC-Score. For example, if a patient's palpebral fissure lengths were 2 or more standard deviations below the norm (≤ -2 SD) and their philtrum and upper lip received Likert scores of 2 and 3 respectively, the facial phenotype would receive an ABC-Score of **CAB**.

5-Point Likert Scale for Philtrum & Lip	Z-score for largest Palpebral Fissure Length	Circle the ABC-Scores for: Palpebral Fissure	Philtrum	Upper Lip
4 or 5	≤ -2 SD	**C**	C	C
3	>-2 SD and ≤ -1 SD	B	B	**B**
1 or 2	> -1 SD	A	**A**	A

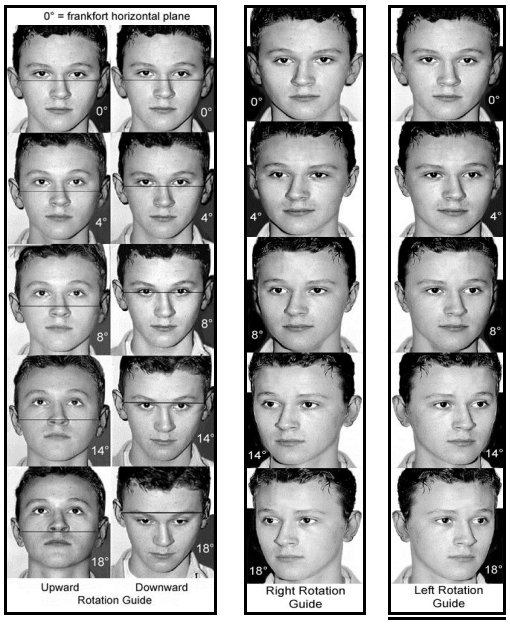
Table 1B. Deriving the 4-Digit Diagnostic Code Rank for the Face.

The final step is to convert the ABC-Score for Facial Phenotype to a 4-Digit Diagnostic Code Rank. A **CAB** score translates into a 4-Digit Diagnostic Code rank of **2.** This rank would serve as the second digit in the 4-Digit Diagnostic Code.

4-Digit Diagnostic Code Rank*	Level of Expression of FAS Facial Phenotype	Palpebral Fissure - Philtrum - Lip ABC-Score Combinations
4	Severe	CCC
3	Moderate	CCB, CBC, BCC
2	**Mild**	CCA, CAC, CBB, CBA, **CAB**, CAA BCB, BCA, BBC, BAC ACC, ACB, ACA, ABC, AAC
1	Absent	BBB, BBA, BAB, BAA ABB, ABA, AAB, AAA

Measuring the Rotation of the Facial Image

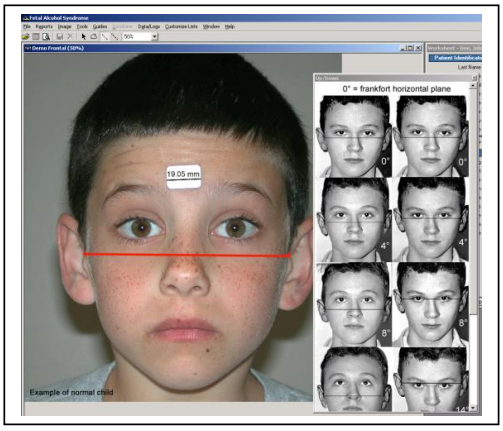
The Rotation Pictorial Guides



Up is (+)
Down is (-)

Right is (+)

Left is (-)



To view: Select from the GUIDES drop-down menu from the top menu bar. When displayed, place the mouse cursor on the guide and hold the left button down to move the Guide over the surface of the facial photograph.

These guides were obtained by placing the subject in a stereotaxic device to achieve accurate measures of rotation in degrees. The most accurate measures of facial features are made from a facial image that has no up, down, right or left rotation. These guides assist you in documenting the magnitude of rotation that may exist in the photograph.

Frontal Image: Ranking Up/Down Rotation

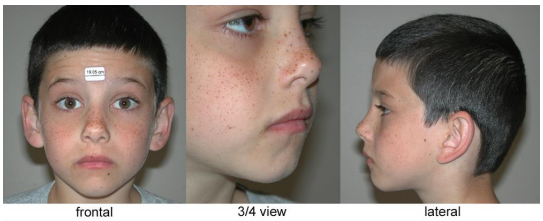
To rank the number of degrees the face in the frontal image is rotated up or down from the Frankfort Horizontal Plane, use the single-distance tool to draw a line from the top of the right tragus to the top of the left tragus in the patient's frontal photograph. See lower left image on this page and the Landmark/Rotation Guide pictured on next page. Compare the position of this line to the position of the lines drawn on the facial images in the Up/Down Rotation Guide. As the face is rotated up the line moves down toward the tip of the nose. As the face is rotated down the line moves up toward the eyebrows. Record your best estimate of the number of degrees of rotation up or down in the proper cell in the Worksheet. You may type in any degree of rotation from -45 to +45 in the cell. You are not restricted to the 5 levels of rotation presented in the Guide.

Frontal Image: Ranking Left/Right Rotation

Use these guides to assist you in judging the number of degrees the subject's head is rotated to their right (+) or their left (-). Record your best estimate of the number of degrees of rotation right or left in the proper cell in the Worksheet. You may type in any degree rotation from -45 to +45 in the cell. You are not restricted to the 5 levels of rotation presented in the Guide.

PART V. ANALYZING AN IMAGE

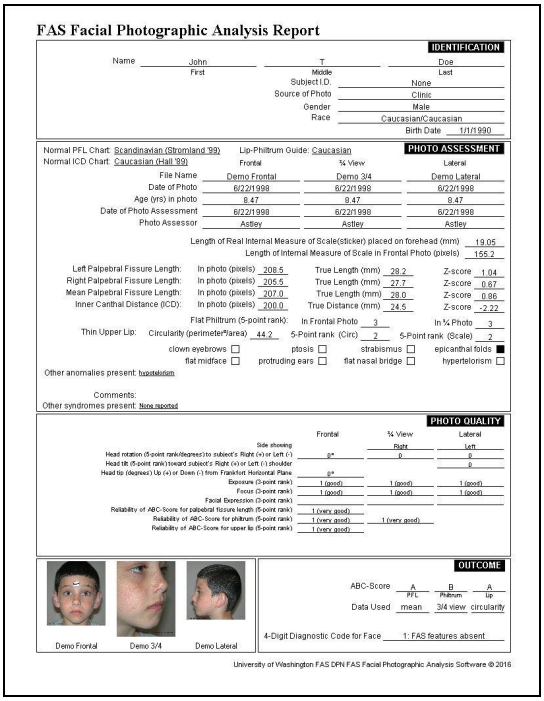
Example of a Complete Analysis and Outcome Report



Standardized Photo Set

This is a child with normal facial features.

An example of a complete analysis and outcome report on the Standardized Photo Set pictured to the left is available for your review. This example is of a child with normal facial features.



FAS Facial Photographic Analysis Report

IDENTIFICATION

Name: John (First) T (Middle) Doe (Last)
Subject I.D.: None
Source of Photo: Clinic
Gender: Male
Race: Caucasian/Caucasian
Birth Date: 1/1/1990

PHOTO ASSESSMENT

Normal PFL Chart: Scandinavian (Stromland '99) Lip-Philtrum Guide: Caucasian
Normal ICD Chart: Caucasian (Hall '99)

	Frontal	¾ View	Lateral
File Name	Demo Frontal	Demo 3/4	Demo Lateral
Date of Photo	6/22/1998	6/22/1998	6/22/1998
Age (yrs) in photo	8.47	8.47	8.47
Date of Photo Assessment	6/22/1998	6/22/1998	6/22/1998
Photo Assessor	Astley	Astley	Astley

Length of Real Internal Measure of Scale(sticker) placed on forehead (mm): 19.05
Length of Internal Measure of Scale in Frontal Photo (pixels): 155.2

Left Palpebral Fissure Length:	In photo (pixels) 208.5	True Length (mm) 28.2	Z-score 1.04
Right Palpebral Fissure Length:	In photo (pixels) 205.5	True Length (mm) 27.7	Z-score 0.67
Mean Palpebral Fissure Length:	In photo (pixels) 207.0	True Length (mm) 28.0	Z-score 0.86
Inner Canthal Distance (ICD):	In photo (pixels) 200.0	True Distance (mm) 24.5	Z-score -2.22

Flat Philtrum (5-point rank): In Frontal Photo 3 In ¼ Photo 3
Thin Upper Lip: Circularity (perimeter²/area) 44.2 5-Point rank (Circ) 2 5-Point rank (Scale) 2

clown eyebrows ☐ ptosis ☐ strabismus ☐ epicanthal folds ■
flat midface ☐ protruding ears ☐ flat nasal bridge ☐ hypertelorism ☐

Other anomalies present: hypertelorism

Comments:
Other syndromes present: None reported

PHOTO QUALITY

	Frontal	¾ View	Lateral
Side showing		Right	Left
Head rotation (5-point rank/degrees) to subject's Right (+) or Left (-)	0*	0	0
Head tilt (5-point rank) toward subject's Right (+) or Left (-) shoulder			0
Head tip (degrees) Up (+) or Down (-) from Frankfort Horizontal Plane	0*		
Exposure (3-point rank)	1 (good)	1 (good)	1 (good)
Focus (3-point rank)	1 (good)	1 (good)	1 (good)
Facial Expression (3-point rank)			
Reliability of ABC-Score for palpebral fissure length (5-point rank)	1 (very good)		
Reliability of ABC-Score for philtrum (5-point rank)	1 (very good)	1 (very good)	
Reliability of ABC-Score for upper lip (5-point rank)	1 (very good)		

Demo Frontal Demo 3/4 Demo Lateral

OUTCOME

ABC-Score A (PFL) B (Philtrum) A (Lip)
Data Used mean 3/4 view circularity

4-Digit Diagnostic Code for Face 1: FAS features absent

University of Washington FAS DPN FAS Facial Photographic Analysis Software © 2016

Outcome Report

To Use: Select File/Open/Existing Subject File from the top menu bar. Double-click on the file named John Doe. Click on the OK button. The frontal, ¾ and lateral facial photos and completed Worksheet will appear for your review and practice. To view the Report, select Reports from the top menu bar. Check the box for the subject named John Doe. Press the Preview button. To print the Report, click on the Print icon on the Tool Bar.

All data in this Sample Case are write-protected so you cannot save any changes you make to the Worksheet or Report.

This Sample Case also serves as a practice case for you. See below for more detailed instructions on how to use this Sample Case as a Practice Case.

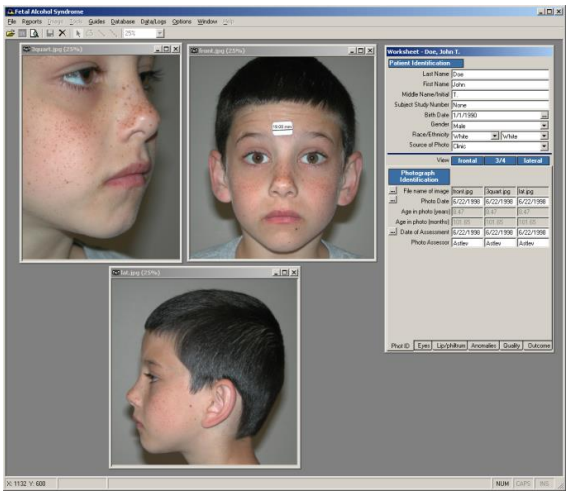
Opening an Image and Worksheet

To Open a New Photo

To Open a New Photo: Select File / Open / Photo from the top menu bar. Navigate through your hard drive to locate the image file you what to measure. Double-click on the image file. A blank Worksheet will automatically open when an image is opened. The Worksheet will not appear if an image is not open.

Typically, you will be analyzing a set of 3 photos (frontal, ¾, and lateral) for each patient. You will find it most efficient to open all three photos before beginning the analysis. You can toggle between the three opened photos by clicking on *Window* in the top menu bar and clicking on the image filename you want to view. More efficiently, once the file names of the 3 photos are entered into the Worksheet, you can click on the blue View banner in the Worksheet labeled Frontal, ¾ and Lateral, just below the Patient Identification section, to view each photo. You may also view all photos at one time by clicking on *Window* in the top menu bar and selecting *Tile Images.*

To Open an Existing Subject File

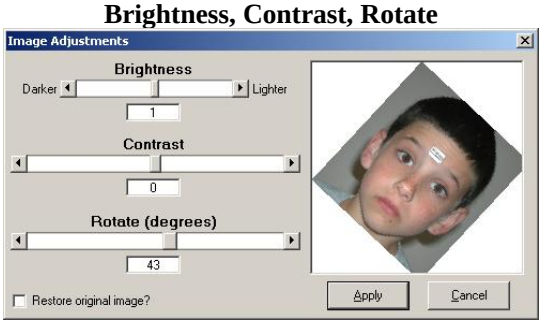


Sample photos of a normal child.

To *Open an Existing Subject File:* Select File / Open / Existing Subject File from the top menu bar. Double-click on the subject's name to highlight it. Then click the OK button. A Worksheet will automatically open with data saved from the previous saved analysis.

Enhancing the Image

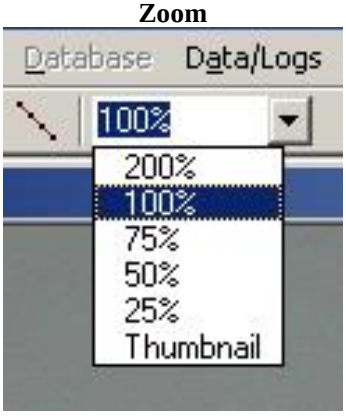
Brightness, Contrast, Rotate



To Use: First open an image. Then select Image / Image Adjustments from the top menu bar.

To adjust *Brightness, Contrast or Rotation* of the image, either slide the control bar from left to right, left-click on the arrows at either end of the slide or type in a positive or negative number in the box below the slide.

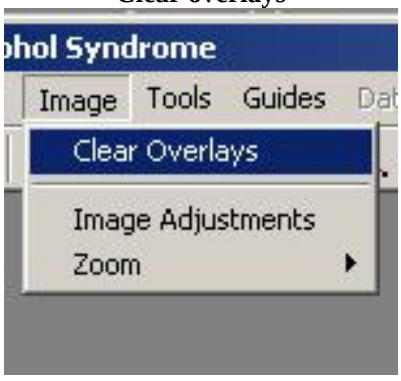
Zoom



To Use: First open an image. Then select Image / *Zoom* from the top menu bar to select a magnification % from the drop-down list or Select a magnification % directly from the drop-down list on the tool bar. You may also type in any incremental number (without a % sign) into the cell next to the down arrow to select intermediate magnification. For example, if you typed 35 in the cell, the image would be presented at 35% magnification. An hour-glass will appear as the magnified image is being generated.

If the image disappears when you enlarge it, you have enlarged it beyond what your video driver can handle. This may occur with very large photos. If this occurs, reduce the zoom incrementally until the image re-appears

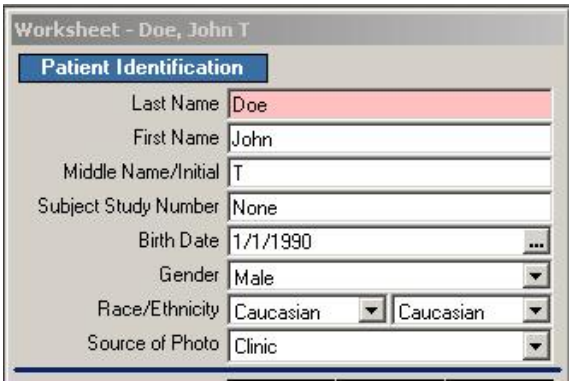
Clear overlays

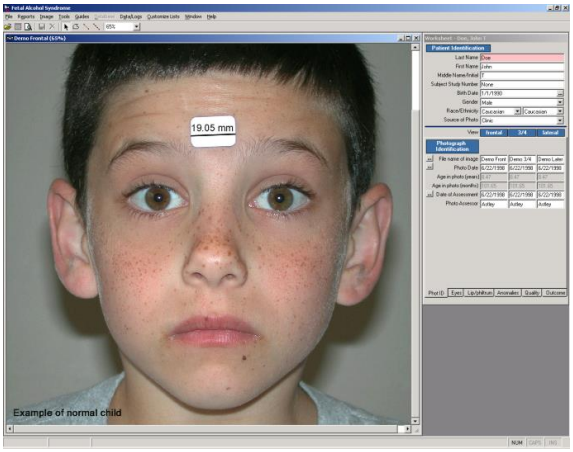


To Use: First open an image. Then select Image / *Clear Overlays fr*om the top menu bar. All distance and circularity measurements drawn on the image as temporary overlays will be removed.

Analyzing an Image
Recording Data on a Worksheet

Patient Identification Section of Worksheet





To view: To open a Worksheet, you must first open an image. The Patient Identification section of the Worksheet is always visible when a Worksheet is open. The cell highlighted in pink is the active cell waiting for data entry.

When an image is opened, the image will appear on the left side of the monitor and a blank Worksheet will open on the right side of the monitor.

The first section of the worksheet is labeled: Patient Identification.

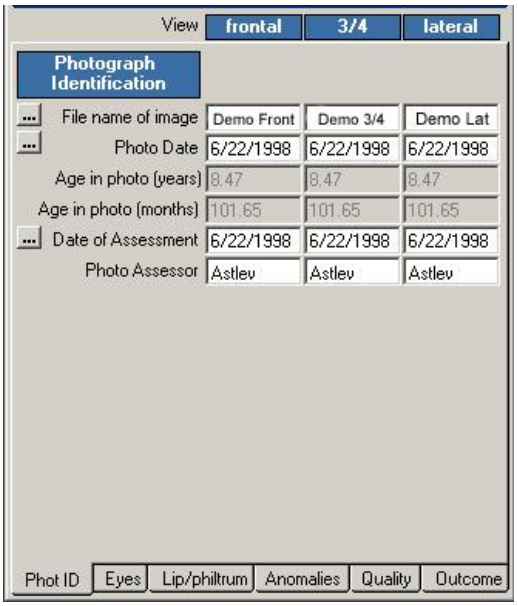
Complete the information by either typing directly into the cells or selecting drop-down menus with the down-arrow.

Dates: Dates can be selected from a calendar by pressing the button on the date line. Click on the calendars year to reveal additional arrows for increasing or decreasing the year. When the correct date is selected, close the calendar and the date will appear in the Worksheet cell. You can also just type the date in the cell. Important: ensure your computer's "Regional Date Setting" is set to English (United States) (mm/dd/yyyy format). See instructions on our website fasdpn.org

Race: Each patient is identified by two races (one for each parent). For example, if both parents are Caucasian, race would be coded Caucasian, Caucasian. If one parent is Caucasian and one is Black, race would be coded Caucasian, Black. Additional races can be added to the drop-down lists by selecting the Customized Lists button on the top menu bar.

Source of Photo: You may want to document the source of the photo (i.e., clinic, research, etc). You can customize the Source of Photo list by selecting the Customized Lists button on the top menu bar.

Photo Identification Section of Worksheet



Once the 'File Name of Image' is entered into the cells for the frontal , ¾ and lateral images, you can click on the BLUE frontal, ¾ and lateral View buttons shown above to view each of those images or toggle back and forth between them.

To View: Select the Photo ID tab at the bottom of the Worksheet.

Photo View: The information requested for the frontal, ¾ and lateral images are presented in the 1st, 2nd and 3rd columns respectively.

File name of image: This is the name you assigned to the electronic facial image. The name of the image file can be typed into the cell or automatically filled in by clicking the mouse in the data cell, (which makes the field active or pink), and then clicking on the opened image. The name of the image file will automatically enter into the active cell. An expedient way to open the three images and enter their filenames automatically into the File Name of Image cells is to 1) open the frontal image and click on the 'File Name of Image' cell for the frontal image. Next, open the ¾ image and click on the 'File Name of Image' cell for the ¾ image. Next, open the lateral image and click on the 'File Name of Image' cell for the lateral image.

Photo Date: This is the date the photo is taken. This date will be used to automatically compute the age of the patient in the photo from the patient's birth date. Your computer's 'Regional Date Setting' must be set to English (United States) for proper age computation (see fasdpn.org for details).

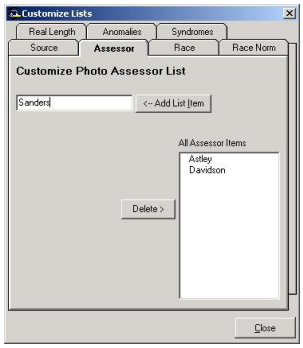
Age in Photo: Age in years and months are grayed out to indicate they will be automatically computed when the birth date and photo date are entered.

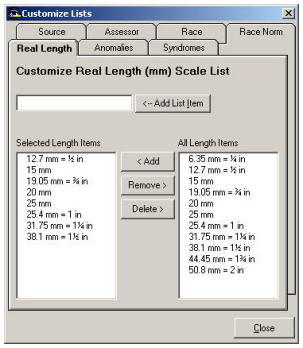
Date of Assessment: This is the date the photograph is being analyzed.

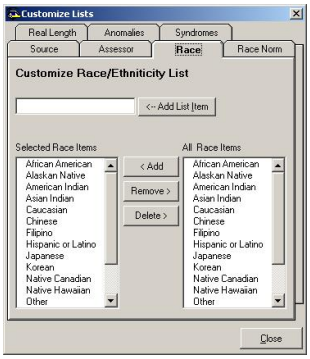
Photo Assessor: This is the name of the person analyzing the photo. This drop-down list can be customized by selecting Customized Lists from the top menu bar.

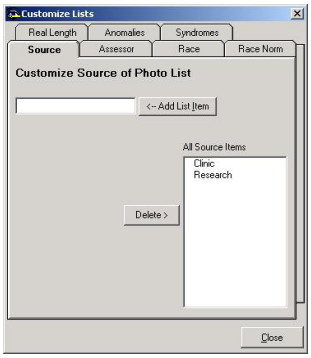
Quick Tip: If the photo date, date of assessment and photo assessor are the same for each image, enter this information for the frontal image, then just click on the Photo Date cell for the ¾ and lateral images and all information from Photo Date to Photo Assessor will automatically fill into the cells.

Customizing Lists









To View: Select "Customize List" from the top Menu Bar.

Each of the following lists can be updated to include additional entries.

Real Length of the internal measure of scale (sticker)
Anomalies
Syndromes
Source of image
Assessor of image
Race of subject
Race Norms for palpebral fissure lengths

To update a list,

1. Click on the appropriate Tab (Lets use Assessor as an example).

2. Type in the new entry in the cell next to "Add List Item". We typed in the name Sanderson.

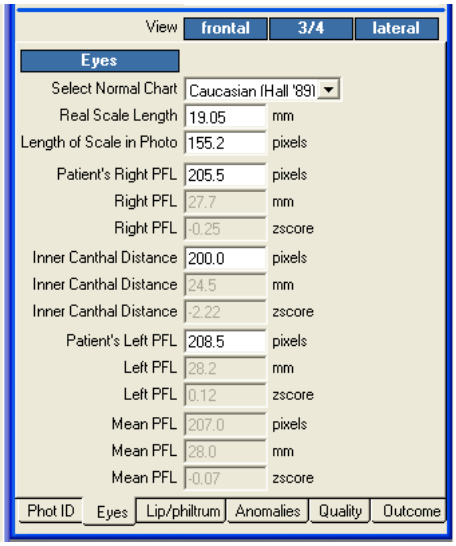
3. Click on the "Add List Item" button. This will add the name Sanderson to our list of assessors.

4. Click on the "Close" button.

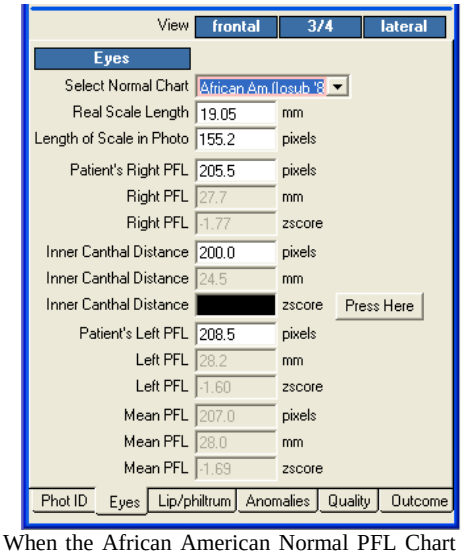
The Race Norms tab is currently inactive. Please refer to the section below entitled "**Importing New Racial Calculations for PFL Z-scores**" for instructions on how to import the new Canadian and Scandinavian PFL formulas. In future versions of this software, additional racial norms for palpebral fissure lengths may be added as norms are established. Currently, racial norms are available for Caucasian (Hall et al., 1989), Canadian (Clarren et al., 2010; Scandinavian (Stromland et al., 1999; and African American (Iosub et al., 1985) palpebral fissure lengths.

Selection of the proper PFL grow charts is very important. The Iosub charts should be used for African Americans. We recommend the Stromland charts for Caucasians. See our website fasdpn.org for more details on which PFL growth charts to use.

Eyes Section of Worksheet



When the Caucasian, Canadian, or Scandinavian Normal PFL Charts are selected, the z-score for Inner Canthal Distance (ICD) is computed using the Hall (1989) normal charts. Z-scores require birth date, photo date, and gender to be entered because all z-scores are age dependent and some are gender dependent.



When the African American Normal PFL Chart is selected, PFL z-scores require birth date, photo date, and gender to be entered. Inner Canthal Distance z-scores are not available for African Americans.

To View: Select the Eyes tab at the bottom of the Worksheet. All eye measurements are obtained from the frontal image.

Only data fields in white are to be filled-in by you. Click the mouse cursor in a white cell to enter data. It will turn pink to designate it is the active cell. Gray fields are computed automatically.

Normal Chart Race: Select the race that best matches the most predominant race of the patient. This selection determines which normal anthropometric chart is used to compute PFL z-scores. Four racial selections are available in Version 2: Caucasian (Hall et al, 1989); Canadian (Clarren et al., 2010), Scandinavian (Stromland et al., 1999), and African American (Iosub et al., 1985). Inner Canthal Distance normal charts are only available for Caucasian (Hall et al., 1989). See our website (fasdpn.org) for guidance on which PFL charts to use.

Real Scale Length: Select the real length of the internal measure of scale (sticker) placed on the patient's forehead. This list can be customized by selecting Customized List from the top menu bar.

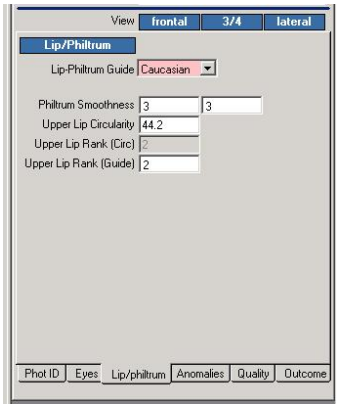
Length of Scale in Photo: This is the horizontal length of the sticker measured in units of pixels using the Single-Distance tool. First click on the image, then click on the Single-Distance Tool, then click on the Length of Scale in Photo cell (it will turn pink when selected), then measure the length of the sticker. See direction above under Single-Distance Tool.

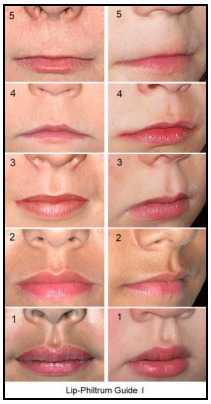
The remaining three data fields are measured using the 3-Distances Tool.

Patient's Right PFL: ___ (pixels)
Inner Canthal Distance: ___ (pixels)
Patient's Left PFL: ___ (pixels)

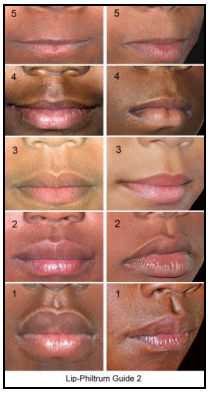
When this tool is selected, data will automatically enter into the R. PFL, Inner Canthal Distance and L. PFL cells in that order, thus they must be measured in that order. With the left mouse button, click on the patient's R. exocanthion, R. endocanthion, L. endocanthion and L. exocanthion in that order. The gray cells will compute automatically based on the birth date, photo date, gender and the race of the normal anthropometric chart selected.

Lip / Philtrum Section of Worksheet





Guide 1



Guide 2

To View: Select the Lip/Philtrum tab at the bottom of the Worksheet.

Photo View: The information requested for the frontal and ¾ images are presented in the 1st and 2nd columns respectively. You can conveniently view the frontal, ¾ and lateral images by clicking on the Blue frontal, ¾ and lateral View buttons.

Lip-Philtrum Guide (Race): Use the drop-down menu to select which Lip-Philtrum Guide is most appropriate to use based on the subject's race(s). Guide 1 is for Caucasians and races with lips like Caucasians. Guide 2 for Blacks and races with thicker lips similar to Blacks.

Philtrum Smoothness: Open a racially appropriate Lip-Philtrum Guide by clicking on GUIDES in the top menu bar. Use this Guide to select which rank on the 5-Point Scale best matches the philtrum smoothness in the patient's frontal and ¾ photos. Philtrum smoothness is most accurately measured from the ¾ view photo. Assign the same philtrum rank for the ¾ and frontal photos. You can move the Guide across the patient's photos by placing the mouse cursor on the Guide and holding the left mouse button down and dragging.

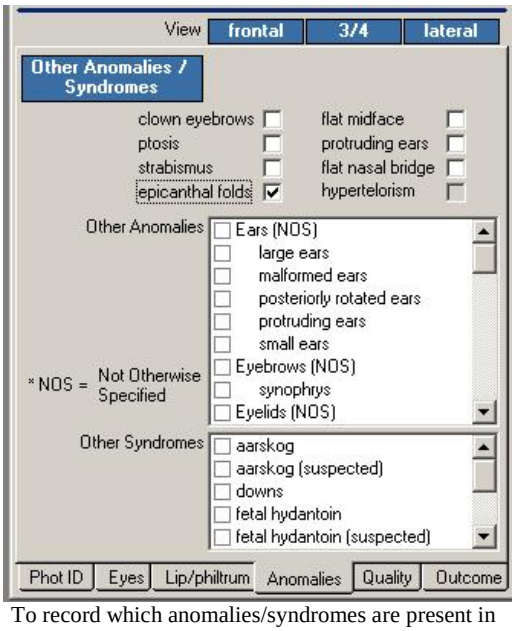
Upper Lip Circularity: Upper lip thinness is most accurately measured using the Circularity Tool. Open the Circularity Tool from the tool bar and measure lip circularity in the frontal photo as instructed above under the Lip Circularity Tool. The circularity of the lip will automatically enter into this field.

Lip thinness is ranked on a 5-Point scale. There are two ways to achieve this: 1) compute the rank automatically from the circularity or 2) judge the rank based on the best pictorial match on the Lip-Philtrum Guide. You will have the option of selecting which method you want to use for ultimately scoring the face under the Outcome Tab.

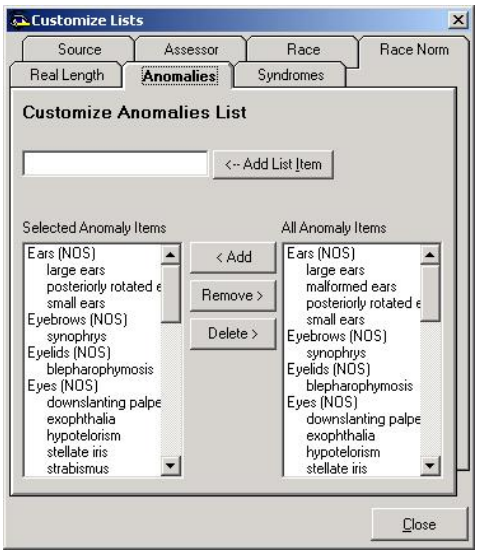
Upper Lip Rank (circularity): The Rank of the upper lip thinness will be automatically computed from the circularity measure and entered into this grayed-out cell. The Rank will be based on which racial Lip-Philtrum Guide you selected. Note, if you toggle between the two Guides, the Rank based on circularity will update to reflect which Guide is selected.

Upper Lip Rank (guide): Use the Lip-Philtrum Guide to select which picture on the 5-Point Scale best matches the lip thinness in the patient's photograph.

Other Anomalies / Syndromes Section of Worksheet



To record which anomalies/syndromes are present in an individual subject.



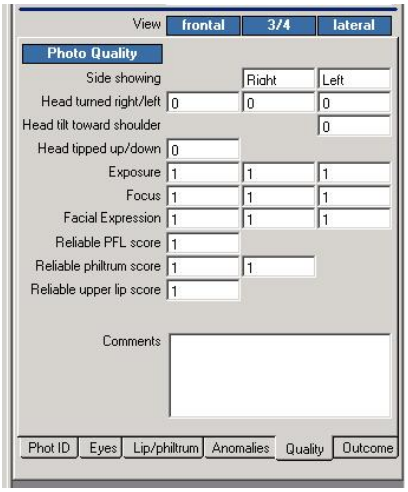
To add new anomalies or syndromes to the list presented under the Anomalies Tab in the Worksheet.

To Use: Select the Anomalies tab at the bottom of the Worksheet.

Anomalies: Place a ✓ in the box next to the anomaly(ies) that the patient has. This list can be customized to include additional anomalies. Go to Customized Lists on the top menu bar and select the Anomalies tab. The additional anomalies you add to the customized list will appear at the end of the Other Anomalies List in the Worksheet. Hypertelorism will automatically get checked if the z-score for the inner canthal distance is ≥ + 2.0. Hypotelorism will automatically get checked if the z-score for the inner canthal distance is ≤ -2.0.

Syndromes: Place a ✓ in the box next to any other syndromes that are known or suspected to be present. This list can be customized to include additional syndromes. Go to Customized Lists on the top menu bar and select the Syndromes Tab. The additional syndromes you add to the customized list will appear in alphabetical order in the Other Syndromes list on the Worksheet.

Photo Quality
Section of Worksheet



To View: Select the Quality tab at the bottom of the Worksheet.

Photo Quality
The quality of a photo will impact the accuracy of the facial measures. The quality of the photo should be taken into consideration when rendering a clinical decision. Photos of poor quality should not be used.

It is recommended that you take some practice photos of a person with widely varying quality (severe rotation, big smile, eyes not fully open, etc) and compare the measures you obtain from those photos with the measures you obtain from a high quality photo of the same individual. This will give you a good idea how much the quality of a photo can impact measurement accuracy.

Photo View: The information requested for the frontal, ¾ and lateral images are presented in the 1st, 2nd and 3rd columns respectively. Not every column requires information.

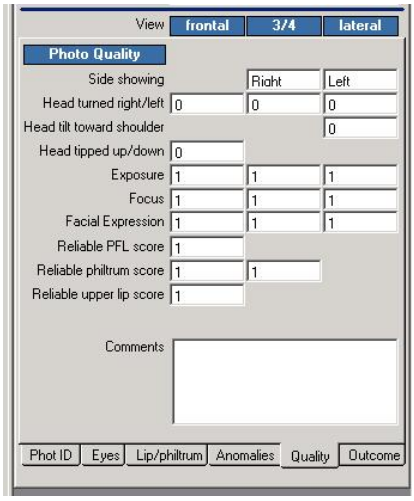
Side Showing: Record whether the right or left side of patient's face is showing in the ¾ and lateral photos.

Head Turned Right / Left in Frontal Image: Use the drop-down menu to record how many degrees the patient's face is rotated toward their right (+) or left (-) in the frontal photo. Use the Right and Left Rotation Pictorial Guides to assist you. You may type in any whole number degree rotation from –45 through +45.

Head Turned Right / Left in ¾ Image: Use the drop-down menu to record how much (on a 5-point scale) the patient's face is rotated toward their right (+) or left (-) in the 3/4 photo. There is no pictorial guide to assist you. Mild rotation implies the amount of rotation present will have only a small impact on the accuracy of the measures obtained from that image. Severe rotation implies the amount of rotation present will have a marked impact on the accuracy of the measures obtained from that image. A ¾ view photo that is rotated too far right or left could impact your ability to accurately measure the smoothness of the philtrum.

Photo Quality Section of Worksheet

(Continued)



Head Turned Right / Left in Lateral Image: Use the drop-down menu to record how much (on a 5-point scale) the patient's face is rotated toward their right (+) or left (-) in the lateral photo. There is no pictorial guide to assist you. Mild rotation implies the amount of rotation present will have only a small impact on the accuracy of the measures obtained from that image. Severe rotation implies the amount of rotation present will have a marked impact on the accuracy of the measures obtained from that image. The measure most likely to be impacted is flat midface. A lateral photograph of the left side of the face that is rotated toward the subject's left will make the midface appear flatter than it truly is. If the same photo was rotated to the subject's right, the midface would appear less flat than it truly is.

Head Tilt Toward Shoulder in Lateral Image: Use the drop-down menu to record how much (on a 5-point scale) the patient's head is tilted toward their left or right shoulder. There is no pictorial guide to assist you. Mild rotation implies the amount of rotation present will have only a small impact on the quality of the measures obtained from that image. Severe rotation implies the amount of rotation present will have a marked impact on the quality of the measures obtained from that image. The measure most likely to be impacted is flat midface.

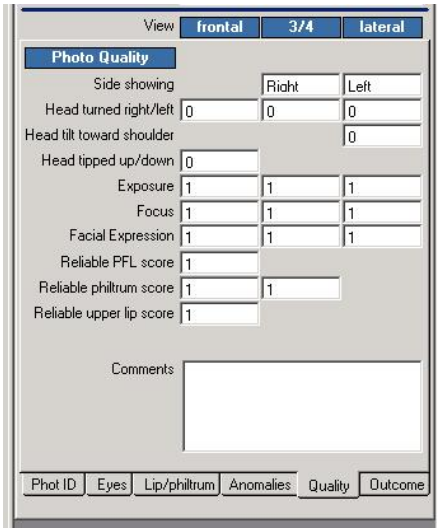
Head Tipped Up / Down in Frontal Image: Use the drop-down menu to record how many degrees the patient's face is tipped up or down in the frontal photo. Use the Up/Down Rotation Pictorial Guide to assist you. You may type in any degree of rotation from –45 through +45 using your best judgement.

Exposure: Use the drop-down menu to record on a 3-point scale if the photo has good exposure, is a bit light/dark or is too light/dark.

Focus: Use the drop-down menu to record, on a 3-point scale, if the photo has good focus, is a bit blurry or is too blurry.

Photo Quality Section of Worksheet

(Continued)

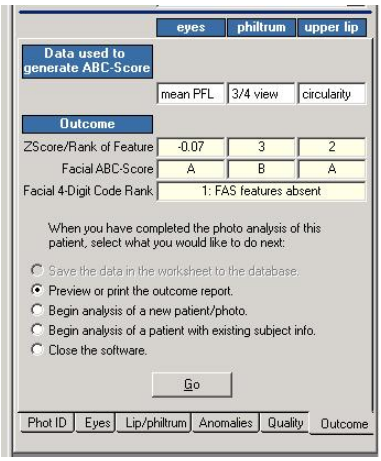


Facial Expression: Use the drop-down menu to record, on a 3-point scale, if the facial expression is relaxed, has a mild facial expression or a severe facial expression. Facial expressions (like a big smile or eyes that are not fully open) can impact measurement accuracy. The goal is to have a relaxed face.

Reliable PFL, Philtrum and Upper Lip Scores. Use the drop-down menus to record, on 5-point scales, if the quality of the photographs leads to reliable ABC and 4-Digit scores for each of these three diagnostic features.

Comments: Enter any comments you wish to have recorded in the database and Outcome Report.

Outcome Section of Worksheet



To Use: Select the Outcomes tab at the bottom of the Worksheet.

Outcome: This last section provides the final scores for the facial phenotype.

Data used to generate ABC-Score: You have the option of selecting which data you would like to use to generate the Facial ABC-Score and 4-Digit Rank. For example, click on the mean PFL cell and note that you can select R.PFL, L.PFL or mean PFL from a drop-down menu. Your selection should be based on which source of information provided you with the most accurate data.

Eyes: You have the option to select the mean PFL, right PFL or left PFL to generate the z-score. The mean PFL is recommended because it will adjust for any right-to-left rotation that may exist in the photo. On rare occasion, the quality of the photo or a true asymmetry in the size of the right and left PFL requires that just the right or left PFL be selected rather than the mean. If there is a true asymmetry in the size of the two PFLs, (> 2 mm's) AND there is NO right-to-left rotation in the frontal image, choose the largest and/or most normal PFL rather than using the mean of the two PFLs.

Philtrum: You have the option to use the philtrum rank from the frontal or the ¾ view photo. Often the ¾ view provides a more accurate measure.

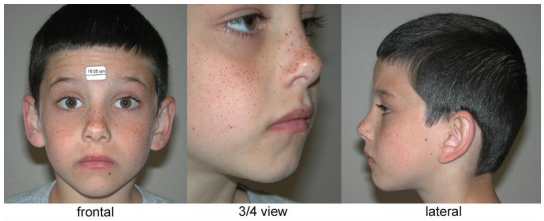
Upper lip: You have the option to have the upper lip be ranked from the circularity measure or from the best matched picture on the Lip-Philtrum Guide. Circularity is often the more accurate measure.

Z-score/Rank of Feature: The z-score or rank of each feature will automatically fill into the cell based on which source of data you chose to use to generate the ABC-Score.

Facial ABC-Score: This score is automatically computed. A is normal, B is moderately abnormal, C is abnormal. (See Astley, 2004a)

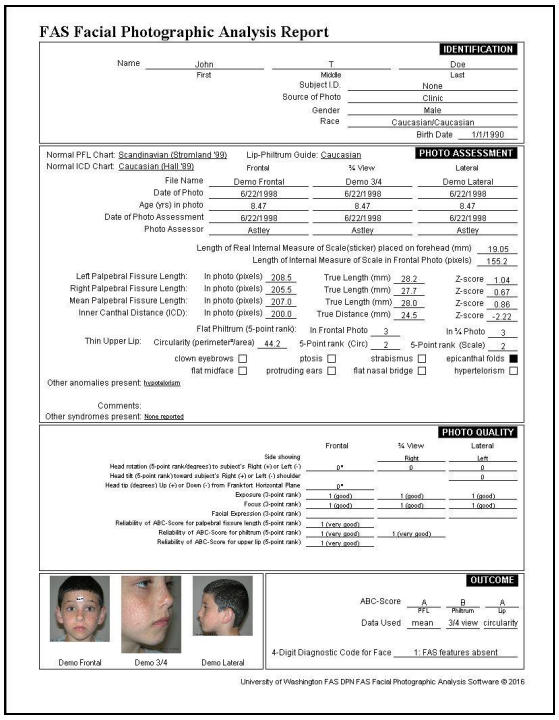
Facial 4-Digit Rank: This score is automatically computed. Rank 1= FAS features absent; Rank 2 = FAS features mild; Rank 3 = FAS features moderate; Rank 4 = FAS features severe. (See Astley 2004a)

Practice Image Set "John Doe"



Standardized Photo Set

This case, John Doe, serves as a Practice Case.
This is an example of a normal child.
The Identification data inserted in the Report is fictitious



FAS Facial Photographic Analysis Report

IDENTIFICATION

Name: John (First) T (Middle) Doe (Last)
Subject I.D.: None
Source of Photo: Clinic
Gender: Male
Race: Caucasian/Caucasian
Birth Date: 1/1/1990

PHOTO ASSESSMENT

Normal PFL Chart: Scandinavian (Stromland '99) Lip-Philtrum Guide: Caucasian
Normal ICD Chart: Caucasian (Hall '89)

	Frontal	¾ View	Lateral
File Name	Demo Frontal	Demo 3/4	Demo Lateral
Date of Photo	6/22/1998	6/22/1998	6/22/1998
Age (yrs) in photo	8.47	8.47	8.47
Date of Photo Assessment	6/22/1998	6/22/1998	6/22/1998
Photo Assessor	Astley	Astley	Astley

Length of Real Internal Measure of Scale(sticker) placed on forehead (mm): 19.05
Length of Internal Measure of Scale in Frontal Photo (pixels): 155.2

Left Palpebral Fissure Length:	In photo (pixels) 208.5	True Length (mm) 28.2	Z-score 1.04
Right Palpebral Fissure Length:	In photo (pixels) 205.5	True Length (mm) 27.7	Z-score 0.67
Mean Palpebral Fissure Length:	In photo (pixels) 207.0	True Length (mm) 28.0	Z-score 0.86
Inner Canthal Distance (ICD):	In photo (pixels) 200.0	True Distance (mm) 24.5	Z-score -2.22

Flat Philtrum (5-point rank): In Frontal Photo 3 In ¾ Photo 3
Thin Upper Lip: Circularity (perimeter²/area) 44.2 5-Point rank (Circ) 2 5-Point rank (Scale) 2

clown eyebrows ☐ ptosis ☐ strabismus ☐ epicanthal folds ■
flat midface ☐ protruding ears ☐ flat nasal bridge ☐ hypertelorism ☐

Other anomalies present: hypotelorism

Comments:
Other syndromes present: None reported

PHOTO QUALITY

	Frontal	¾ View	Lateral
Side showing		Right	Left
Head rotation (5-point rank/degrees) to subject's Right (+) or Left (-)	0°	0	0
Head tilt (5-point rank) toward subject's Right (+) or Left (-) shoulder			0
Head tip (degrees) Up (+) or Down (-) from Frankfort Horizontal Plane	0°		
Exposure (3-point rank)	1 (good)	1 (good)	1 (good)
Focus (3-point rank)	1 (good)	1 (good)	1 (good)
Facial Expression (3-point rank)			
Reliability of ABC-Score for palpebral fissure length (5-point rank)	1 (very good)		
Reliability of ABC-Score for philtrum (5-point rank)	1 (very good)	1 (very good)	
Reliability of ABC-Score for upper lip (5-point rank)	1 (very good)		

Demo Frontal Demo 3/4 Demo Lateral

OUTCOME

ABC-Score: A (PFL) B (Philtrum) A (Lip)
Data Used: mean 3/4 view circularity

4-Digit Diagnostic Code for Face: 1: FAS features absent

University of Washington FAS DPN FAS Facial Photographic Analysis Software © 2016

Practice Case Report for John Doe

To Use: Select File/Open/Existing Subject File from the top menu bar. Double-click on the file named John Doe. Click on the OK button. The frontal, ¾ and lateral facial photos and a completed Worksheet will appear for your review and practice. To view the Report, select Reports from the top menu bar. Check the box for the subject named John Doe. Press the Preview button. To print the Report, click on the Print icon on the Tool Bar.

The purpose of this practice case is to allow you to practice using the measurement tools to see if you can duplicate the outcomes of key measures like:

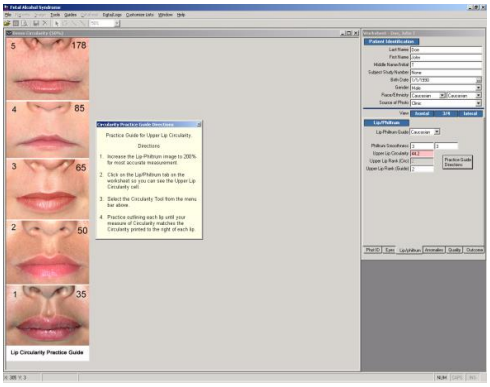
Left PFL = 208.5 pixels
Right PFL = 205.5 pixels
Inner Canthal Distance = 200.0 pixels
Internal Measure of Scale = 155.2 pixels
Lip circularity = 44.2
Philtrum smoothness = Rank 3

It is recommended you first print the report to use as a Guide, because once you start altering data in the Worksheet, your alterations will be reflected in the Report.

Even though you can alter the data in the Worksheet and Report, you will not be able to save the altered data. This will protect the Practice Case for future use and reference.

To refresh the Practice Case to its original data, go to the Outcome Tab on the Worksheet, select *Begin analysis of a patient with existing subject info* and click on GO. Double click on John Doe and press the OK button. A refreshed version of the Practice Case will appear on our screen.

Circularity Practice Guide



Circularity Practice Guide presented with the Directions visible and the Upper Lip Circularity cell highlighted pink.

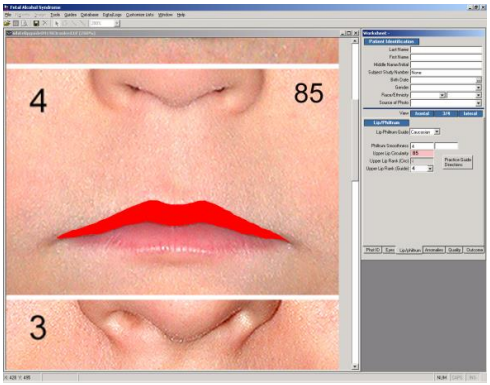


Image zoomed to 200% for measuring circularity.

To Use: Select Guides / Circularity Practice Guide from the top menu bar. The Lip-Philtrum Guide 1 will appear for you to practice outlining.

For Directions:

1. Click on the "Practice Guide Directions" button showing in the Lip/Philtrum window of the Worksheet.
2. Increase the Lip-Philtrum Guide to 200% for most accurate measurement.
3. Select the Circularity Tool from the top menu bar. Notice the Upper Lip Circularity cell is pink.
4. Practice outlining the red portion of the upper lip until your measure of circularity repeatedly matches the circularity printed to the right of each lip photo. Note that your outline should reach from the left to the right corners of the mouth.
5. Each time you select the Circularity tool to outline a lip; a window will appear alerting you that "There is already an upper lip circularity value. Do you want to overwrite it?" Say Yes.
6. To end the session, click on the Outcomes Tab at the bottom of the worksheet and click on "Begin analysis of new patient/photo".

Tips:

Note that more accurate, reproducible measures can be achieved when the image is increased in size (up to 200% zoom). The circularity of the lip does not change with magnification, but your ability to outline it accurately will. Try measuring the same lip at 50%, 100% and 200% zoom to see for yourself.

Adjust your mouse tracking specifications to achieve maximum hand-mouse control.

Test your ability to outline the same lip and get the same circularity each time. See our website (fasdpn.org) for an animated example of lips being outlined.

Consider outlining a subject's lip 2 or 3 times and taking the average across the multiple measures to obtain the most accurate measure of circularity.

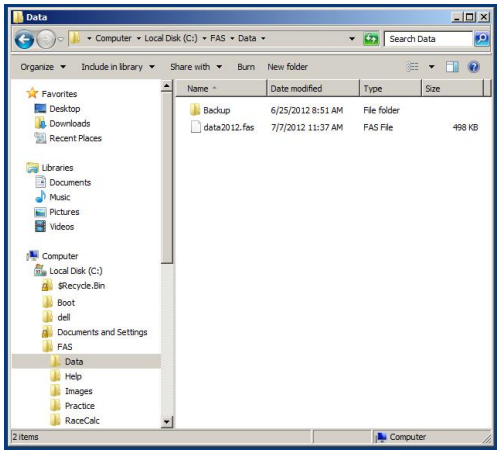
PART VI. SAVING / DELETING / EXPORTING THE DATA

The Facial Software Database

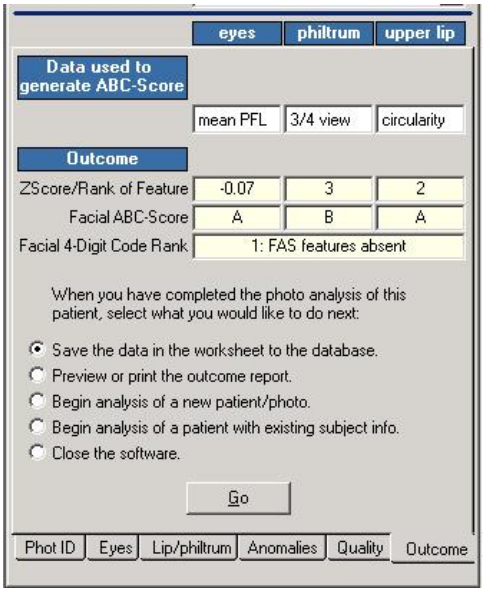
This software program comes with a Microsoft Access database that is specifically designed to store all photo analysis data displayed in the Worksheet, if you choose to save it. The database does NOT store the digital facial photos. Your digital photos are stored in a directory on your hard drive per your specifications. The Access database stores the path that locates where the digital photo was stored on your hard drive, at the time you saved the Worksheet. This stored path allows the database to retrieve the digital photo and display it in the Report, when you ask to view the Report. This stored path also allows the software to locate your photos if you choose to evaluate them again at a later date. The software will not be able to find and display the digital photos if you change their location on your hard drive after you saved the Worksheet data.

When you analyze a set of photographs for a patient, the data is displayed in the Worksheet. When you save the data in the Worksheet, it is saved as a single Record in the database, linked to the patient's last name, birth date, and the file names of up to three images (frontal, ¾ and lateral). If you analyze a second set of photographs for a patient, perhaps photos taken at a different age, this second Worksheet would be saved as a second record for that patient.

The Access database that stores the photo analysis data is named **data2012.fas** by default, when you install the software. Note that this database is saved on your hard drive under C:\FAS\data2012.fas. If you reload the software, an empty data2012.fas file will be installed and overwrite your existing data2012.fas file that contains all your photo analysis data. **Thus, it will be VERY important that you rename the data2012.fas file on your hard drive, and preferably copy the renamed file onto your desktop for safe keeping, before reinstalling the software**. Please see detailed directions for installing the software on our website fasdpn.org.



Saving the Data in the Worksheet to the Facial Software Database



There are two methods to save the data in the Worksheet to the Facial Software Database:

Method 1:

1. Click on the Outcome Tab at the bottom of the Worksheet
2. Click on "*Save the data in the worksheet to the database*".
3. Click the "*GO*" button.

Method 2:

1. Highlight the Worksheet
2. Select *Database* from the top menu bar.
3. Select "*Save current worksheet data from database*.

Deleting Data in the Database

To delete data from the Database:

1. Open the case you want to delete.
2. Click on the top border of the Worksheet.
3. Select *Database* from the top menu bar
4. Select *Delete current worksheet data from database"*.

Exporting Data from the Database

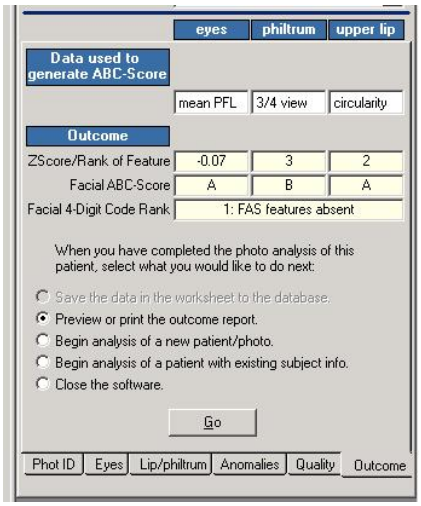
To export one or many patient records into a comma-delimited text file:

1. Select *File* from the top menu bar.
2. Select *Export Records.*
3. In the left window in the pop-up window that appears, browse to the directory where you would like to save the exported file. By default, the exported file will be placed in C:\FAS\Export directory.
4. In the *File Name* box, type in the name you would like to call the exported file. It will automatically be assigned ".txt" as an extension.
5. Click the *Save* button.
6. In the next window, you will see a list of patients whose records have been saved. Double-click on the patient you want to highlight it. If you want to select multiple patients, you may hold down the Ctrl key and click (highlight) as many names as you wish. If you want to select all of the patients, click on the first name, scroll down to the end of the list, hold down the Shift key, and click on the last name.
7. Click the *Export* button.

PART VII. VIEWING / PRINTING THE OUTCOME REPORT AND DATABASE MANAGEMENT

Viewing the Outcome Report

Method 1

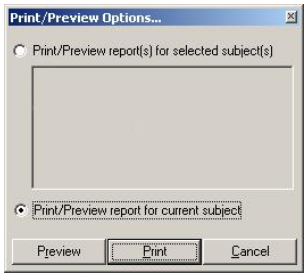


There are two methods to view the Outcome Report.

1. Select the Outcome Tab and select "Preview or Print outcome report"

   A copy of the current subject's Outcome Report will appear.

Method 2



Selecting the current subject's Report

Selecting a previous subject's saved Report

2. Select Report from the top menu bar to open the "Print/Preview Options" window.

   To Select the Current Subject's Report

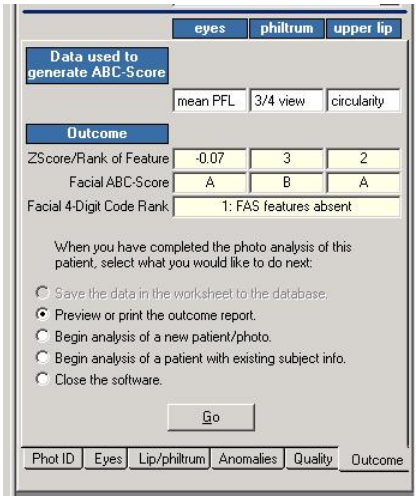
   To preview the Report of the subject whose data is currently showing in the Worksheet, select *Print/Preview report for current subject.*

   To Select Previous Subjects' Reports

   To preview the Report(s) of previous subjects whose data was saved to the Facial Software Database, select *Print/Preview report(s) for selected subject(s).*

Printing the Outcome Report

Method 1



There are two methods to print the Outcome Report

1. Select the Outcome Tab and select "Preview or Print outcome report"

   A copy of the current subject's Outcome Report will appear.

   Click on the Print button in the top menu bar.

Method 2

Printing the current subject's Report

Printing a previous subject's saved Report

2. Select Report from the top menu bar to open the "Print/Preview Options" window.

   To Print the Current Subject's Report

   To print the Report of the subject whose data is currently showing in the Worksheet, select *Print/Preview report for current subject.*

   Then click on the Print button.

   To Print Previous Subjects' Reports

   To preview the Report(s) of previous subjects whose data was saved to the Facial Software Database, select *Print/Preview report(s) for selected subject(s).*

   Then click on the Print button.

FAS Facial Photographic Analysis Report

IDENTIFICATION

Name	John (First)	T (Middle)	Doe (Last)
Subject I.D.	None		
Source of Photo	Clinic		
Gender	Male		
Race	Caucasian/Caucasian		
Birth Date	1/1/1990		

PHOTO ASSESSMENT

Normal PFL Chart: Scandinavian (Stromland '99) Lip-Philtrum Guide: Caucasian
Normal ICD Chart: Caucasian (Hall '89)

	Frontal	¾ View	Lateral
File Name	Demo Frontal	Demo 3/4	Demo Lateral
Date of Photo	6/22/1998	6/22/1998	6/22/1998
Age (yrs) in photo	8.47	8.47	8.47
Date of Photo Assessment	6/22/1998	6/22/1998	6/22/1998
Photo Assessor	Astley	Astley	Astley

Length of Real Internal Measure of Scale(sticker) placed on forehead (mm) 19.05
Length of Internal Measure of Scale in Frontal Photo (pixels) 155.2

Left Palpebral Fissure Length:	In photo (pixels) 208.5	True Length (mm) 28.2	Z-score 1.04
Right Palpebral Fissure Length:	In photo (pixels) 205.5	True Length (mm) 27.7	Z-score 0.67
Mean Palpebral Fissure Length:	In photo (pixels) 207.0	True Length (mm) 28.0	Z-score 0.86
Inner Canthal Distance (ICD):	In photo (pixels) 200.0	True Distance (mm) 24.5	Z-score -2.22

Flat Philtrum (5-point rank): In Frontal Photo 3 In ¾ Photo 3

Thin Upper Lip: Circularity (perimeter²/area) 44.2 5-Point rank (Circ) 2 5-Point rank (Scale) 2

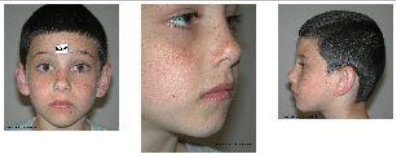
clown eyebrows ☐ ptosis ☐ strabismus ☐ epicanthal folds ■
flat midface ☐ protruding ears ☐ flat nasal bridge ☐ hypertelorism ☐

Other anomalies present: hypotelorism

Comments:
Other syndromes present: None reported

PHOTO QUALITY

	Frontal	¾ View	Lateral
Side showing		Right	Left
Head rotation (5-point rank/degrees) to subject's Right (+) or Left (-)	0°	0	0
Head tilt (5-point rank) toward subject's Right (+) or Left (-) shoulder			0
Head tip (degrees) Up (+) or Down (-) from Frankfort Horizontal Plane	0°		
Exposure (3-point rank)	1 (good)	1 (good)	1 (good)
Focus (3-point rank)	1 (good)	1 (good)	1 (good)
Facial Expression (3-point rank)			
Reliability of ABC-Score for palpebral fissure length (5-point rank)	1 (very good)		
Reliability of ABC-Score for philtrum (5-point rank)	1 (very good)	1 (very good)	
Reliability of ABC-Score for upper lip (5-point rank)	1 (very good)		



Demo Frontal Demo 3/4 Demo Lateral

OUTCOME

	PFL	Philtrum	Lip
ABC-Score	A	B	A
Data Used	mean	3/4 view	circularity

4-Digit Diagnostic Code for Face 1: FAS features absent

University of Washington FAS DPN FAS Facial Photographic Analysis Software © 2016

Report for Practice Case John Doe

Database Management

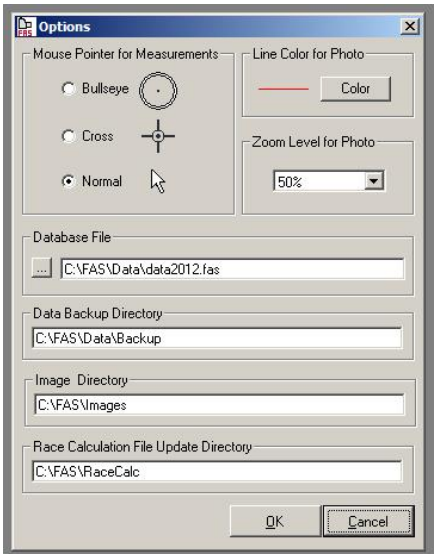


Fig. 7. Options box opened from the Tools tab on the top menu bar.

To Use: Select Data/Logs from the top menu bar and select Database Management from the drop-down menu.

The following database management tools are provided.

1. **Database File**
   Allows you to navigate to the **.fas** database you want to store your photo analysis data in.
2. **Backup Data**
   The Backup Data option makes a backup file of the database currently displayed in the 'Database File' window in the Options box (Fig. 7). The backup file will be named with the date you backed it up followed by data.bak. For example, if you pushed the backup button on July 16, 2012, the file would be named (**7-16-2012data.bak**). This backup file will be stored in the directory displayed/selected in the 'Data Backup Directory' window in the Options box (Fig. 7). If your database file becomes corrupted, you can restore it from any backup files you made.
3. **Restore Data**
   If something happens to the database file you are currently working with [(e.g., the file designated in the Database File window in the Options box (Fig. 7)], the Restore Data option lets you choose from any backup files you may have made and **overwrites** the database file you are currently working with [e.g., the file designated in the Database File window in the Options box (Fig. 7)]), with the restored backup file. The restored database file will only contain data stored before the backup was made. If you have not made any backup files, you will not be able to use this function.
4. **Compact Data**
   The Compact Data option packs data more efficiently in the database file, resulting in a smaller file size. The FAS Facial Analysis software does this for you automatically every time you open the program.
5. **Import New Racial Calculations**
   In future versions, we anticipate providing you with additional racial norms for PFL and inner canthal distance. These new norms would be imported into the software via this route. Please see more about importing new racial calculations below.
6. **Set Password**
   The software program may be password protected with this feature.

View Logs

To Use: Select Data/Logs from the top menu bar and select View Logs from the drop-down menu.

The following logs document all activity regarding Errors, Back up and Restoration.

1. Error Log
2. Back up Log
3. Restore Log

Importing New Racial Calculations for PFL Z-scores

FAS Version 1.0 provided palpebral fissure length (PFL) z-score formulas for Caucasians and African Americans. FAS Version 2.0 software provides PFL z-score formulas for Caucasians, African Americans, Canadians, and Scandinavians. It is important to understand that these formulas are stored IN THE SAME DATABASE as your photo analysis data. The Caucasian and African American formulas are stored in the **data.fas** database for Version 1.0. The Caucasian, African American, Canadian, and Scandinavian formulas are stored in the **data2012.fas** database for Version 2. If you open an older database (e.g., **data.fas**) created by Version 1.0 into the new Version 2 software, the new PFL formulas to compute Canadian and Scandinavian PFL z-scores will be missing. You will discover this when you go to the Eye Tab in the software Worksheet and click on the drop-down menu for "Select Normal PFL Chart". Only Caucasian and African American PFL Charts will be available.

But it is simple to import the new Canadian and Scandinavian PFL z-score formulas into your older Version 1.0 **data.fas** database.

Follow these instructions:

1. It is assumed that the FAS Facial Software Version 2 is open and the Database File selected in the Options window (Fig 3 above) is pointing to an older **data.fas** database that does not currently have the Canadian and Scandinavian PFL formulas in it.
2. Click on the menu item: Data/Logs → Database Management → Import New Racial Calculations.
3. On the **Select File for Update** dialog box, select **the Canadian Male.rcf** file located in C:\FAS\RaceCalc\ and click the **Open** button. (See Fig. 8)
4. A message box will appear showing "New racial calculations have been successfully imported". Click the **OK** button.
5. Repeat step 3, but this time select the **Canadian Female.rcf** file and click the Open Button.
6. A message box will appear again confirming the upload. Click the **OK** button. (See Fig. 8)
7. Click on the menu item: Data/Logs → Database Management → Import New Racial Calculations.
8. On the **Select File for Update** dialog box, select **the Scandinavian Male.rcf** file located in C:\FAS\RaceCalc\and click the **Open** button. (See Fig. 8)
9. A message box will appear showing "New racial calculations have been successfully imported". Click the **OK** button.
10. Repeat step 3, but this time select the **Scandinavian Female.rcf** file and click the Open Button.
11. A message box will appear again confirming the upload. Click the **OK** button (See Fig. 8).
12. Re Start the FAS Facial Software.
13. Go to the Eye Tab in the software Worksheet and click on the drop-down menu for "Select Normal PFL Chart". You should now see all four PFL options available.
14. See our website (fasdpn.org) for guidance on which PFL charts to use.

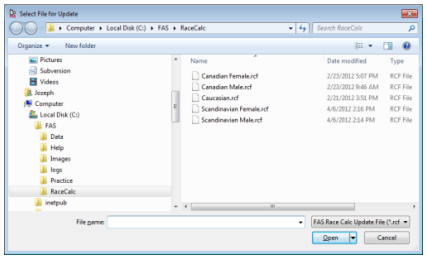


Fig. 8.

DICTIONARY

Anomaly
: A physical feature that is present in less than 2% of an age and race appropriate sample of the population

Circularity
: A quantitative measure (perimeter^2/area) used to objectively measure upper lip thinness. The thinner the upper lip, the greater the circularity. See the Lip Circularity Table on the backside of the Lip-Philtrum Guides.

Clown eyebrows
: Eyebrows that arch upward at the lateral margins. The eyebrow typically follows the superior border of the bony orbital rim. Clown eyebrows are often secondary to microcephaly. See the FAS Face / Other Anomaly Pictorial Guide.

Endocanthion
: The facial landmark demarcating the inner corner of the eye fissure where the eyelids meet. See the Landmark / Rotation Pictorial Guide.

Epicanthal fold: Lateral extension of skin of the nasal bridge over the endocanthion landmark. May be unilateral or bilateral. May be indigenous to some races. More common in very young children of all races. See the Landmark / Rotation Pictorial Guide.

Exocanthion
: The facial landmark demarcating the outer corner of the eye fissure where the eyelids meet. See the Landmark / Rotation Pictorial Guide.

External auditory canal
: The external opening of the ear canal. This is one of two landmarks that demarcate the Frankfort Horizontal plane when viewing the lateral facial photograph. See the Landmark/Rotation Pictorial Guide.

Flat (hypoplastic) midface
: Under-development of the maxilla relative to the nasal process.

Flat nasal bridge
: The bridge of the nose between the eyes is depressed (flattened). May be indigenous to some races and is more common in very young children of all races. See the FAS Face / Other Anomaly Pictorial Guide.

Frankfort horizontal plane
: A plane demarcated by a line drawn from the external auditory canal to the lowest border of the bony orbital rim (orbitale). This plane is used in anthropometry to standardize the positioning of the head. For the purposes of measuring FAS facial features, the camera lens should be placed in the patient's frankfort horizontal plane. See the Landmarks/Rotation Pictorial Guide.

Hypertelorism

Ocular hypertelorism is an abnormal increased distance between the centers of the pupils. This term is also often used to denote an abnormal increased distance between the right and left endocanthion landmarks (or telecanthus).

Hypotelorism

Ocular hypotelorism is an abnormal decreased distance between the centers of the pupils. This term is also often used to denote an abnormal decreased distance between the right and left endocanthion landmarks.

Inner Canthal Distance

The distance between the eyes from the right endocanthion to the left endocanthion. See the Landmark/Rotation Pictorial Guide.

Internal Measure of Scale

The paper sticker (typically ½ to ¾ inch) placed on the patient's forehead to serve as a ruler or internal measure of scale in the photograph. This allows the true PFL and inner canthal distances to be computed. See the Landmark/Rotation Pictorial Guide.

Orbitale

The lowest point on the bony orbital rim. This is one of two landmarks that demarcate the Frankfort Horizontal plane. See the Landmark/Rotation Pictorial Guide.

Overlay

A term used in this software program that refers to the lines that are temporarily drawn on the photograph when distance or circularity measures are being taken. These overlays can be removed from the photograph by clicking on Image/Clear Overlays in the Menu bar.

Palpebral fissure length (PFL)

A measure of the size of the eye. The distance from the exocanthion to the endocanthion landmarks. See the Landmark/Rotation Pictorial Guide.

Phenotype

Physical appearance.

Philtrum

The vertical groove between the nose and upper lip. See the Landmarks/Rotation Pictorial Guide.

Pixels

A unit of measure used in computerized image analysis. A pixel is one dot of light on the computer monitor.

Ptosis

Drooping of upper eyelid. Generally caused by a weakness in the levator palpebrae superious muscle. See the FAS Face / Other Anomaly Pictorial Guide.

Thin upper lip (or thin vermilion border)

When measuring the thinness of the upper lip, the part of the upper lip that is being referred to is the red or vermilion portion of the upper lip. See the Landmarks/Rotation Pictorial Guide.

Tragus

A small extension of tissue in front of the external auditory canal. This is one of two landmarks that demarcate the Frankfort Horizontal plane when viewing the frontal facial photograph. See the Landmark/Rotation Pictorial Guide.

Z-score

The z-score reflects how many standard deviations above or below the population mean the patient's PFL is, based on the patient's age and gender. The z-score is defined as the patient's PFL minus the mean PFL for the normal population divided by the standard deviation of the mean PFL for the normal population.

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Purkinje Cell Deficits in Nonhuman Primates Following Weekly Exposure to Ethanol During Gestation

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ABSTRACT The most serious features of fetal alcohol syndrome (FAS) are mental retardation and other behavioral problems resulting from alcohol-induced damage to the developing central nervous system (CNS). The mechanism by which alcohol induces its neuroteratogenic effects is unknown. One hypothesis is that gestational alcohol exposure results in a reduction in neuronal number. This study demonstrates that gestational exposure to ethanol in a non-human primate species induces permanent dose-related deficits in the number of cerebellar Purkinje cells. Ethanol was administered via nasogastric tube once per week to 15 gravid pigtailed macaques (Macaca nemistrina) in one of the following doses: 0.0 (intubated controls), 1.2, 1.8, 2.5, 3.3, and 4.1 g/kg/dose. Offspring were reared with parental surrogates and were sacrificed at 6 months of age; 8-μm-thick parasagittal sections were cut through the paraffin-embedded cerebellar vermis. Purkinje cells were quantified, the length of the Purkinje cell line was determined stereologically, and Purkinje cell linear frequency was calculated. The number of Purkinje cells and their linear frequencies were significantly reduced in the alcohol-treated subjects, and the deficits were dose-dependent. The groups receiving 2.5 g/kg/dose and above were most severely affected and had an average deficit in Purkinje cell number of 11.8%, relative to controls. Alcohol had no effect on the length of the Purkinje cell line. The findings suggest that alcohol-induced reduction in neuronal number may be an important factor underlying the CNS dysfunction in FAS.

Ethanol abuse during pregnancy can have adverse effects on the developing fetus and, in severe cases, results in fetal alcohol syndrome (FAS) (Jones and Smith, '73; Jones et al., '73). The most serious features of FAS are mental retardation and other behavioral abnormalities resulting from damage to the developing central nervous system (CNS) (Clarren, '86; Streissguth et al., '80).

Despite the fact that alcohol abuse is one of the leading known causes of mental retardation in the western world (Abel and Sokol, '91), there is a paucity of human data available concerning the neuroanatomical changes resulting from fetal alcohol exposure. Because FAS was only recently recognized as a distinct clinical entity, and because the syndrome is not usually fatal, few fetuses or infants with recognized FAS have undergone autopsy. Those few autopsied cases that have been published generally describe extreme CNS damage (Clarren, '86; Claren et al., '78). However, many of these cases were accompanied by confounding complications, such as severe congenital heart defects and by maternal abuse of other drugs, making it difficult to determine whether the observed CNS anomalies were due to alcohol directly or to the confounding factors.

The mechanism by which fetal alcohol exposure induces postnatal CNS dysfunction is unknown. One hypothesis is that alcohol exposure results in a reduction in neuronal number—either through interference with neuronal production or through induction of neuronal death—and that the resulting neuronal deficits underlie or contribute to the CNS dysfunction. Through the use of animal models, deficits in neuronal number following developmental alcohol exposure have been demonstrated in the hippocampus (Barnes and Walker, '80), somatosensory cortex (Miller and Potempa, '90), cerebellum (Hamre and West, '93), retina (Clarren et al., '90) and olfactory bulb (Bonthius et al., '92). Furthermore, ethanol-induced neuronal loss has been dem-

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onstrated in regions known to influence specific behaviors, and these behaviors have been shown to be abnormal in animals with these neuronal deficits. For example, spatial memory deficits have been correlated with loss of CA1 pyramidal cells in the hippocampus (Goodlett et al., '92). Such results support the hypothesis that neuronal loss associated with ethanol exposure is functionally important.

Nearly all the evidence demonstrating neuronal deficits following developmental alcohol exposure has been derived from rodent models of FAS. The question arises whether the alcohol-induced neuronal deficits in the brains of rats and mice are relevant to the human condition.

Several inherent constraints limit the widespread use of nonhuman primates in biomedical research. Animals are expensive and difficult to acquire; they have long gestational periods, and pre- and postnatal care is complicated. Nevertheless, primate models offer advantages of evaluating the effects of gestational alcohol exposure on the fetus (Riley and Meyer, '84). Among these advantages are the important facts that nonhuman primates are more similar to humans developmentally, ontogenetically, neuroanatomically and behaviorally than are rodents (Bourne, '75; Golub, '79; Hendrickx and Sawyer, '75).

The principal goal of this study was to determine whether prenatal exposure to ethanol can induce permanent neuronal deficits in a primate species. The neuronal population examined in this study is the cerebellar Purkinje cells, a group of neurons known to be exquisitely vulnerable to alcohol-induced cell death in developing rats (Bonthius and West, '90).

The exposure paradigm in the present study was designed to mimic common drinking patterns in humans. Consumption of ethanol once per week has been found to be the most frequent intermittent pattern of drinking by American women (Wilsnack et al., '84). Since the pattern of ethanol exposure during development influences the risk and severity of brain damage (Bonthius and West, '90; Webster et al., '83), it is important to model conditions similar to which a human fetus is likely to be exposed. Therefore, the gravid monkeys in this study were exposed to intoxicating levels of ethanol on a weekly basis.

METHODS

Subjects

The cerebellar tissue evaluated in this study was derived from 15 animals generated as part of a larger project at the University of Washington, the methods and results of which have been described previously (Clarren et al., '88, '90). Ethanol was administered via nasogastric tube once per week to gravid pigtailed macaques (*M. nemestrina*). The ethanol doses were 1.2 (n = 1), 1.8 (n = 4), 2.5 (n = 2), 3.3 (n = 3), and 4.1 (n = 1) g/kg/dose. Animals that were exposed to the lower doses (1.2 and 1.8 g/kg) of ethanol were nasogastrically intubated weekly throughout gestation (weeks 1–24), while animals exposed to the higher doses (2.5–4.1 g/kg) received the ethanol starting with the fifth week of gestation. Delay in administration of the higher doses was necessary because earlier work showed that the higher doses produced insufficient viable offspring in the time allotted for the experiments when administered throughout gestation (Clarren et al., '88). A control group of gravid females (n = 4) received a weekly oral sucrose solution that was isocaloric and isovolumetric to the highest ethanol dose.

Maternal peak plasma ethanol concentrations

Blood samples were taken from each pregnant female once every 8 weeks (three times per pregnancy), and plasma ethanol concentrations were determined as previously described (Clarren et al., '87). The three serum ethanol concentrations for each animal were averaged to provide a mean maternal peak plasma ethanol concentration (MPPEC). The complete MPPEC data for each of these animals have been published previously (Clarren et al., '88).

Tissue preparation

The offspring were reared independently of their mothers, were housed with parental surrogates (diapers) and had daily social experience with groups of like-aged peers. After participating in extensive physical and behavioral evaluations, the offspring were sacrificed at approximately six months of age (329–380 days postconception). Following sedation by intramuscular injections of ketamine, an intravenous line was placed in the saphenous vein through which chloral hydrate was infused. When a deep level of anesthesia was reached, cranial nerves and spinal cord were severed, and the brain was carefully removed. The cerebellar peduncles were cut, separating the cerebellum from the brainstem. The cerebellum was wrapped in gauze and placed in 10% neutral buffered formalin to await further processing.

A 2-mm-thick sagittal slice was taken from each cerebellar vermis. The cuts were made parallel to and 1 mm to either side of the midline so that the entire midcerebellum was included. The 2-mm-thick slices were dehydrated through a series of alcohols, cleared in xylene and embedded in paraffin. Each slice was oriented to allow sectioning in the parasagittal plane.

The blocks were cut as 8-micrometer-thick sections on a rotary microtome, and a 1-in-5 series of sections was saved. The sections were floated in a 37°C water bath for 10 sec, mounted onto gelatin-coated slides and allowed to dry overnight at room temperature. The sections were stained with a combination of safranin O and cresyl violet, dehydrated, cleared in xylene, and coverslipped with Permount.

Cell counting and estimation of line length

From the set of sections saved, three sections from each subject which were free of folds and tears were

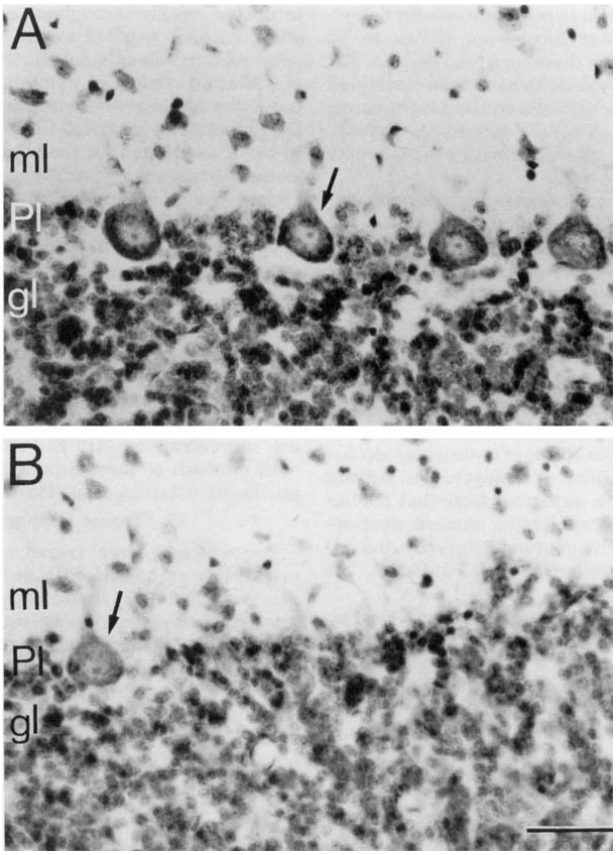

Fig. 1. Photomicrographs of cerebellar cortex from 6-month-old pigtailed macaques. **A:** From a control animal exposed to no alcohol during gestation. The arrow points to a typical Purkinje cell body. Purkinje cells with clearly discernible nuclear membranes were counted in three representative sections per animal. Note that the Purkinje cells in this control section are spaced quite closely together along the length of the Purkinje cell line. **B:** From an animal exposed to weekly doses of 3.3 g/kg of alcohol during gestation. The alcohol exposure has resulted in a diminishment of Purkinje cell number. The deficit in Purkinje cells manifests itself as large gaps in the Purkinje cell line in which few Purkinje cells exist. **Arrow,** points to the only surviving Purkinje cell in this segment of cortex. ml, molecular layer; Pl, Purkinje cell layer; gl, granule cell layer. Bar = 25 μm.

randomly chosen for analysis. In each analyzed section (Fig. 1), Purkinje cells with clearly discernible nuclear membranes were counted manually (Bonthius and West, '90, '91).

In order to determine the length of the Purkinje cell line, a magnified (×125) image of the section was projected onto a square grid consisting of parallel lines separated by a distance of 1 cm. The intersections that the Purkinje cell layer made with each of the two sets of parallel lines making up the grid were counted. The number of intersections (I) provided a direct and unbiased estimate of the length (L) of the Purkinje cell line according to the formula (Harvey and Napper, '88; Weibel, '79):

$$L = I \times \pi/4 \times D \times 1/M$$

where, in this case, D is 1 cm and M is 125. The linear frequency of Purkinje cells was derived by dividing the number of Purkinje cells by the length of the Purkinje cell line.

TABLE 1. Maternal peak plasma ethanol concentrations (MPPECs)[1]

Weekly alcohol dose (g/kg/dose)	n	Gestational weeks of exposure	MPPEC (mg/dl)
0.0	4	1–24	
1.2	1	1–24	140.5 ± 3.5
1.8	4	1–24	208.4 ± 29.1
2.5	2	5–24	262.3 ± 23.4
3.3	3	5–24	431.6 ± 74.4
4.1	1	5–24	548.3 ± 87.8

[1]All measures represent means ± S.D.

Nuclear diameters

In order to correct for potential changes in nuclear fragment number due to differences in nuclear size, the distribution of nuclear fragments was estimated from random, systematically chosen samples of Purkinje cell populations. The long and short axes of each sampled nucleus were measured under oil immersion with a gradicule eyepiece. The axes of 400 nuclear fragments per treatment group were measured. The geometric means of the axial measurements were calculated, pooled, and plotted as nuclear fragment diameter frequency histograms.

Statistical analyses

Cell counts were made from three sections from each animal. For the statistical analyses, the values from each of the three sections were averaged. The number of Purkinje cells per section, Purkinje cell line length, and Purkinje cell linear frequency were analyzed separately by simple linear regression (Wonnacott and Wonnacott, '77). The nuclear diameter frequency histograms were analyzed by chi-square test.

RESULTS

Table 1 demonstrates that the MPPECs ranged from 140.5 mg/dl in the animal exposed to the lowest alcohol dose (1.2 g/kg) to 548.3 mg/dl in the animal exposed to the highest alcohol dose (4.1 g/kg). As expected, as the dose of alcohol increased, so did the MPPEC rise in a stepwise fashion.

The cerebellums of two subjects (one each in the 3.3- and 4.1-g/kg groups) were mechanically damaged during processing; several small lobules were broken and lost. As a result, it was not possible to determine accurately the total number of Purkinje cells per section nor the Purkinje cell line length for these two subjects. It was possible, however, to determine the Purkinje cell linear frequency on the remaining undamaged tissue from these two subjects. Therefore, the data regarding total Purkinje cell number and line length were derived from 13 subjects, while the data regarding Purkinje cell linear frequency were derived from 15 subjects. The mean number of Purkinje cells per section, estimated Purkinje cell line length and calculated Purkinje cell linear frequency for each of the animals is shown in Table 2.

TABLE 2. Purkinje cell number, Purkinje cell line length, and Purkinje cell linear frequency for individual animals[1]

Subject no.	Weekly ethanol dose (g/kg)	Purkinje cell no.	Purkinje cell line length (mm)	Purkinje cell linear frequency (cells/mm)
1	0.0	2202	368	6.00
2	0.0	2371	422	5.62
3	0.0	2346	404	5.82
4	0.0	2467	399	6.18
5	1.2	2421	416	5.83
6	1.8	2084	376	5.45
7	1.8	2156	398	5.42
8	1.8	2457	397	6.19
9	1.8	2279	442	5.13
10	2.5	2103	377	5.58
11	2.5	1995	373	5.34
12[2]	3.3	1582	279	5.68
13	3.3	2189	416	5.27
14	3.3	1996	378	5.29
15[2]	4.1	1576	301	5.20

[1]All measures represent the mean values from three analyzed sections.
[2]Subjects in which the cerebellum was mechanically damaged during processing, resulting in the loss of several small lobules. In these subjects, only the Purkinje cell linear frequency could be determined accurately and was included in the statistical analyses.

Alcohol exposure during gestation induced dose-dependent Purkinje cell deficits. The regression analysis indicated a significant effect of ethanol dose on Purkinje cell number [$F(1,11) = 8.164$; $P < 0.05$]. As shown in Figure 2A and in Table 2, the subjects exposed to the highest doses (2.5 and 3.3 g/kg) were the most severely affected and had an average deficit in Purkinje cell number of 11.8%, relative to controls. A strong inverse correlation existed between the ethanol dose and Purkinje cell number ($r = -0.653$).

The regression analysis also indicated a significant effect of ethanol dose on Purkinje cell linear frequency [$F(1,13) = 9.59$; $P < 0.01$]. As shown in Figure 2B, as the dose of ethanol increased, the linear frequency of Purkinje cells tended to decrease linearly.

The alcohol-induced deficits in Purkinje cell number and linear frequency manifested themselves as gaps in the Purkinje cell line. Whereas control animals had a relatively frequent and uniform presence of Purkinje cells throughout the Purkinje cell line, the alcohol-exposed animals had segments of cortex in which few Purkinje cells existed (Fig. 1). Although the location of these gaps was not systematically analyzed, they seemed to occur in a random pattern, unrelated to any particular rostrocaudal position, cerebellar lobule, or depth within the folia.

The ethanol treatment had no significant effect on the length of the Purkinje cell line (Fig. 2C), indicating

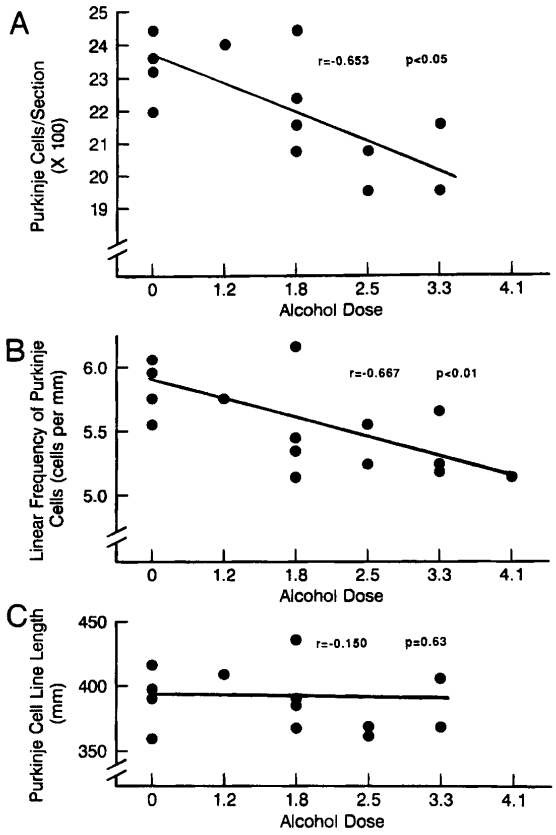

Fig. 2. Effect of gestational alcohol exposure on the number of Purkinje cells, Purkinje cell linear frequency and length of the Purkinje cell line. **A:** Dose-response effect of alcohol on the number of Purkinje cells per sagittal section. Gestational alcohol exposure induced dose-dependent Purkinje cell deficits, with the animals exposed to the highest doses (2.5 and 3.3 g/kg) being most severely affected. **B:** Dose-response effect of alcohol on Purkinje cell linear frequency. As the dose of alcohol increased, the linear frequency of Purkinje cells tended to decrease. **C:** Relationship of alcohol dose to length of the Purkinje cell line. Increasing doses of alcohol had no significant effect on the length of the Purkinje cell line.

that the alcohol-induced reduction in Purkinje cell number was not merely due to a reduced length of cortex along which the cells were counted.

Examination of nuclear fragment diameter frequency histograms indicated no significant differences in modal diameter or in the distribution of diameters among the treatment groups (Fig. 3).

DISCUSSION

The most important findings of this study are that ethanol exposure during gestation in monkeys produces dose-dependent cerebellar Purkinje cell deficits and a corresponding decline in Purkinje cell linear frequency. Other than a multidisciplinary report that included some counts of retinal ganglion cells (Clarren et al., '90), this is the first study to report quantitative evidence of dose-dependent neuronal deficits in the nonhuman primate brain as a consequence of fetal ethanol exposure. These findings of diminished Purkinje cell number and linear frequency support the hypothesis that deficits in neuronal number may underlie or contribute to the cognitive and behavioral problems associated with FAS. Indeed, as described in an earlier report (Clarren, Astley and Bowden, '88), many of the alcohol-exposed animals in this study exhibited substantial motor and cognitive deficits and delays.

A second important finding of this study is that neuronal deficits occurred following patterns of alcohol ex-

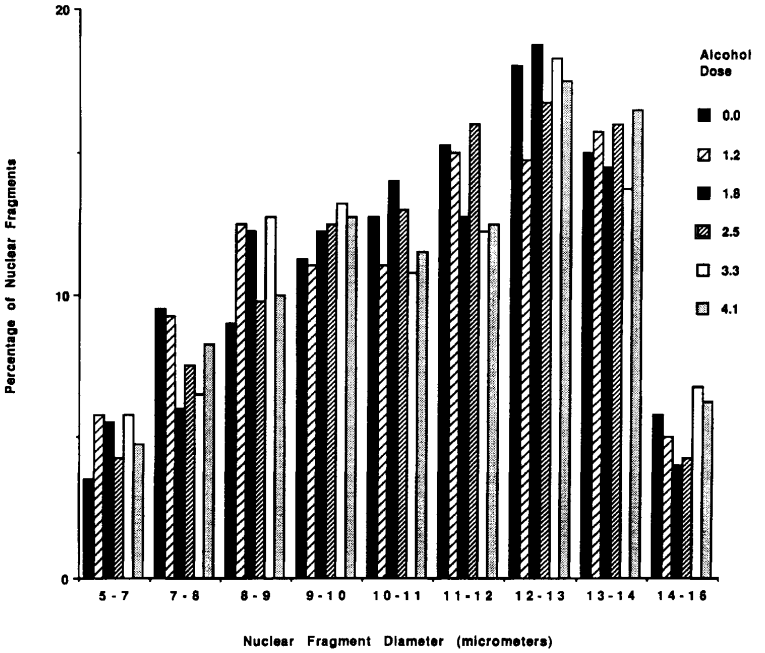

Fig. 3. Nuclear fragment diameter frequency histogram for the Purkinje cell population of 6-month-old pigtailed macaques. The axes of 400 nuclear fragments per treatment group were measured, and the geometric means of the axial measurements were pooled and plotted. The alcohol treatments had no significant effect on the distribution of the nuclear diameters.

posure and blood alcohol concentrations commonly seen in humans. The alcohol in this study was administered once per week. Epidemiological studies have demonstrated that women who drink during pregnancy tend to binge drink—often once per week (Stephens, '85; Little and Streissguth, '78). The findings of the present study demonstrate, as have several rodent studies (Bonthius and West, '90, '91), that binge alcohol consumption during pregnancy can induce substantial and permanent brain injury in the fetus.

The mechanism underlying fetal ethanol-induced damage in general, and Purkinje cell depletion in particular, remains unknown (West et al., '94). Purkinje cells are the earliest generated cells of the cerebellar cortex (Altman and Bayer, '78). In the monkey, Purkinje cell neurogenesis is completed during the first half of pregnancy (Verbitskaya, '69). Since the ethanol exposure in this study occurred throughout all or most of gestation, it encompassed a broad period of brain development including eras preceeding, during and following Purkinje cell neurogenesis. Therefore, the ethanol may have interfered with any of a host of developmental processes upon which the Purkinje cell population depends for generation, differentiation and survival. Ethanol has been shown to interfere with cell proliferation and migration (Borges and Lewis, '83; Miller, '86). However, studies in the rat have shown that Purkinje cells are most vulnerable to alcohol-induced cell death during the period of cellular differentiation—after they have completed the periods of neurogenesis and migration, but before they have reached full maturity (Bonthius and West, '90; Hamre and West, '93; Marcussen et al., '94). Exposure to alcohol for a single day has been shown to be sufficient to kill a substantial number of Purkinje cells during this period of vulnerability (Goodlett et al., '92). In the rat, an altricial species, this period of maximum vulnerability occurs in the early postnatal period (Marcussen et al., '94). The monkey, however, is a precocial species, and its brain is substantially more mature at the time of birth than is the rat's (Dobbing and Sands, '79). Therefore, if maximum vulnerability of the Purkinje cell to alcohol occurs at the same developmental stage of Purkinje cell differentiation in the monkey as it does in the rat, then the monkey Purkinje cell would be expected to be most vulnerable during the final third of pregnancy.

Most of the alcohol-exposed animals in this study, including those exposed to the highest doses of alcohol (≥2.5 g/kg/dose), had no evidence of external dysmor-

phology (for details, see Clarren, Astley and Bowden, 1988). Yet, many of these animals clearly had alcohol-induced neuronal deficits. This finding demonstrates that alcohol-induced brain damage can occur in the absence of external dysmorphology in a primate species and strengthens the troubling notion that children with alcohol-induced brain damage may be far more common than those diagnosable with the full fetal alcohol syndrome.

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Development of the FAS Diagnostic and Prevention Network in Washington State

Sterling Clarren and Susan Astley

Introduction

It has not yet been demonstrated that stories and warnings in the media about the adverse impact of drinking alcohol during pregnancy lead directly to a reduction in the incidence of Fetal Alcohol Syndrome (FAS) and related disorders. However, it has become clear to us that every time a widely viewed piece on FAS appears in the press or on television, there is a sharp increase in requests for appointments for FAS diagnosis. Parents seem to recognize their own children's difficulties in the descriptions of patients with FAS and wonder if FAS is, at last, the elusive answer to the enigma that is their child.

We began to receive requests for FAS diagnoses in the late 1970s after the first major articles on FAS had been published (Clarren & Smith, 1978; Hanson, Jones, & Smith, 1976; Jones, Smith, Ulleland, & Streissguth, 1973) and the first major campaign to improve maternal awareness and decrease alcohol use in pregnancy had been mounted (Little, Streissguth, & Guzinski, 1980). For many years, we attempted to serve these patients' diagnostic needs through referrals to existing clinics at Children's Hospital and Medical Center, in Seattle, Washington. Some patients were evaluated in diagnostic clinics such as Medical Genetics, Dysmorphology, Neurology, or Developmental Disabilities. Others were followed in chronic care clinics like the Craniofacial or Neurodevelopmental Programs.

The feedback we received from both patients and faculty was generally neutral to negative. None of these medical settings seemed to meet the needs of many of the patients. The families recognized almost immediately that whether or not they received a specific diagnosis , they had sought much more. They really wanted help with management across four large domains: medical, psychiatric/psychologic, educational, and social, with recommendations for specific interventions by specific individuals in their locality. Funding was almost always a major concern. Most of our faculty were capable of making an accurate medical diagnosis of FAS, but no program was prepared to evaluate and appropriately treat or refer the patients in a comprehensive fashion for the myriad of functional problems that led to the evaluation in the first place.

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By the late 1980s it became clear that a new clinic was needed to address the long term management needs of patients debilitated by alcohol teratogenesis. The clinic had to be prepared to evaluate patients of all ages and to handle different types of problems in clients of different ages — because FAS produced ongoing needs across the life span. In infants and children below the age of three years or so, the diagnosis was more important for future planning than for any specific intervention at that time. In children of preschool and primary school years, academic and behavioral problems were a major issue. Academic problems were seen as more important, although in middle school years concern over behavioral problems generally outweighed concern over the ongoing academic issues. In older teens and adults, problems of employment, relationships, and independent living were often the primary concerns. Frequently, the patients' specific problems did not meet specific criteria for help as defined by the schools or the social welfare system.

However, if the birth mother of an affected child was able to have more children and was still drinking, she was at high risk to have other children with alcohol-related problems and was at high risk to have alcohol-related health problems of her own. Issues of alcohol abuse and addiction existed in families of patients of all ages, expressed through the mother's feelings about herself, the other family member's feelings about her, and concern for the patient's own susceptibility to alcohol abuse and addiction. The identification of young FAS patients needed to be attached to a program that would reach out and help the birth mothers. This issue had to be identified and dealt with specifically because it affected all other interventions.

It seemed reasonable that the new clinic would work well if it was based on a traditional multi-disciplinary developmental model that would be responsive to patients and caregivers with varying needs in a context of available local services. We found that such a new clinic for FAS patients was not easy to establish. The majority of the assessments and treatments that were needed were not medical, but

social, educational, psychologic, or related to addictions. As long as the clinic was run from a hospital base and billed as a medical service, the financial reimbursement was so low that the clinic was not viable. Beyond fee for service, no other means of funding a service clinic was readily available to us. Unfortunately, if a clinic is never established because there is no funding mechanism, then the value of the clinic cannot be demonstrated and the financial "Catch-22" cannot be understood and corrected.

In 1990, we responded to a Request for Proposal from the Centers for Disease Control and Prevention (CDC). The CDC was looking for innovative approaches to the primary prevention of FAS. We suggested that an immediate reduction in the incidence of FAS could be accomplished by identifying women who had had an FAS child. If these women could be helped to become clean and sober through any subsequent pregnancies, then pregnancies at the highest risk for producing infants with FAS could be avoided. But who were these women, and what factors in their lives needed to be understood for an effective intervention to work? To this time, there have been no published reports describing the lives of mothers of FAS patients as a group in the general population of the United States. It was clear from our personal experience and the general literature that FAS patients frequently did not live with their birth mothers. A clinic that would make regular, accurate, and consistent diagnoses of FAS and related conditions would demonstrate that the mothers could be found. The birth mothers could then be interviewed as a first step in developing a focused intervention plan.

This project was funded by the CDC. We are now in the fourth year of a five year study. The project allowed us to create the FAS Diagnostic Clinic at the University of Washington's Center for Human Development and Disability, which was the beginning of the development of the FAS Diagnostic and Prevention Network of Washington State.

The CDC funding permitted us to schedule the clinic to meet one day per week. We found that four or five patients could be assessed in a clinic day, and between 160 to 180 patients could be evaluated in a year. Our waiting list grew steadily. At times, 500 or more names were on the waiting list. Clearly, we could never see all of the applicants. The fact that so many families requested appointments, and were willing to wait months to be seen, underlined our previous impression that while numerous facilities were available to assess FAS in the context of some specific discipline or another, and that while most of these families had availed themselves of some of these

services, the families still did not believe that their children had been appropriately understood or directed to appropriate services.

We worked with the March of Dimes Foundation for Healthier Babies to establish two FAS Network sites (in King and Snohomish Counties). These sites were based on our clinic model at the University of Washington, the concept of multiple funding sources, and perceived community interest by professionals and families. Our group provided training and data management and the local staff were responsible for patient assessment and treatment planning. At that same time, the Washington State Legislature, responding to lobbying from concerned parents, wished to develop a model for helping with the perceived unmet needs of patients with FAS and their families. We suggested to a state senator, who was drafting legislation, that our FAS Network idea might make sense for the state. The concept was adopted in Senate Bill 5688 that became state law in 1995. The law provided for the development of several additional sites, which currently is ongoing. Funding was made available for development, training, and data management. The sites remain responsible for finding the resources needed to cover patient care costs.

All clinics will function similarly to the clinic established at the University of Washington. The structure of that clinic is described below.

The Clinic

Staff

The *primary staff* are the core group of professionals needed for diagnosis and treatment plan development for all patients. The ideal team comprises individuals from six disciplines: medicine, psychology, speech and language pathology, social work, public health nursing, and family advocacy. The first three members are largely responsible for the assessments necessary to make the diagnosis and develop the treatment plan; the latter three members more often are responsible for helping to implement the plan.

The *secondary staff* are a larger group of professionals that can be called on to consult in specific cases, but would not necessarily be needed in all cases. Staff members might include (but would not be limited to) medical subspecialties like psychiatry, neurology or genetics, alcohol treatment counselors, educators, educational psychologists, behavioral therapists, family therapists, lawyers, and parent support groups.

Referral Process

Referrals are accepted from any primary sources including physicians, teachers, psychologists, social service agencies, the courts, and the families themselves. In order to gauge the appropriateness of the referral, the family is asked to complete an extensive questionnaire. This document asks for information in all areas that will be pertinent to the diagnosis, including gestational history and gestational exposures to drugs and alcohol, basic genetic historical information, and descriptions of medical, social, educational, and behavioral problems. Photos are requested.

The returned questionnaires are reviewed at weekly meetings and the patients are placed in one of three groups:

Group A. The patient has a documented history of exposure to alcohol in utero and there are physical anomalies and behavior problems present. A diagnosis of FAS, a related condition, or another birth defect syndrome is likely.

Group B. The patient has a documented history of alcohol exposure in utero or physical anomalies and/or behavioral problems so that a diagnosis of FAS or a related condition still may be reasonably considered.

Group C. The patient has no documented history of alcohol exposure in utero and no physical anomalies. Although the patient's behavioral problems might be just as serious as are those of patients in groups A and B, it is unlikely that the clinic will be able to link the etiology to ethanol teratogenesis or reach out to a birth mother in hope of preventing subsequent cases.

Patients in groups A and B are scheduled to be seen at the clinic. Because the clinic currently is funded as a research tool aimed at finding the mothers of FAS patients, patients in group A with the highest likelihood of having FAS, and a birth mother still known to be living in Washington State, are given the highest priority. Conversely, patients in group C are sent a letter suggesting that they be evaluated in another setting. Specific alternate settings are suggested when appropriate.

Clinic Process

The patient's evaluation can be divided into five distinct "phases:"

Phase 0: Collection of old records. Phase 0 occurs between the time the referral is accepted for an appointment and the actual clinic day. Most patients who are evaluated in our program already have had multiple evaluations including medical, psychological, educational, and social-welfare reviews. During this waiting period, the clinic coordinator and possibly the family advocate work with the family to identify and locate copies of these materials.

Phase 1: Clinical assessments. This phase involves the collection of new data by team members. At a minimum, this will include an interview with the family and the patient, and a physical exam emphasizing dysmorphological and neurological conditions. If the old records do not contain current and appropriate psychometric test results, then such tests will need to be obtained as well. The most helpful tests usually are IQ measures, tests of academic performance, tests of language usage, and tests of adaptive ability.

Phase 2: Case conference. The staff meets as a whole to discuss the diagnosis(es) and the etiologies of the diagnosis(es), and to develop an initial treatment plan. The family then is invited into the session, the situation is clarified, and the final treatment plan is developed with input from the family.

Phase 3: Debriefing. The family then meets with a single member of the staff, usually the psychologist, to discuss the emotional impact of the clinical day and the diagnosis. We have found that this phase is critical in helping the family to use the information from the clinic in a positive way. After having been "talked at," families need time to "talk back" and process the situation.

Phase 4: Staff closure. After the debriefing period, the psychologist usually needs to finalize the case with the rest of the staff and arrange for any follow-up with team members that was suggested in Phase 3. This also is an appropriate time to insure that all records have been completed.

Diagnostic Schema

The definition of FAS has changed little in the last twenty years (Clarren & Smith, 1978; Rosett, 1980; Sokol & Clarren, 1989). The condition is typified by growth deficiency, a characteristic set of facial features, and evidence of prenatal alteration in brain function such as microcephaly from birth, neurologic problems without postnatal antecedents, or complex patterns of functional disability that cannot be explained or understood solely in terms of postnatal experiences. The condition is distinctive and can be readily separated from normal and almost all other birth defect syndromes by trained observers (Astley & Clarren, 1995; Clarren et al., 1987). The history of alcohol exposure in gestation is not part of the clinical criteria for the diagnosis of FAS, but rather the history of alcohol supports the diagnosis.

For the trained clinician, there is little difficulty in making the diagnosis of FAS when the abnormalities in growth, face, and brain

are all extreme, and the alcohol exposure history is conclusive and substantial. But the features of the condition are not dichotomous; the clinical features and, indeed, the history of alcohol exposure itself each range along a separate continuum from normal to clearly abnormal. Accurately and fairly characterizing intermediate conditions has posed difficulties. To date, clinicians have not agreed on a simple diagnostic schema to deal with the gradations in exposure and in effects.

In our clinic, several diagnostic terms initially were used to deal with this problem. These are:

FAS with confirmed history of alcohol exposure. These patients met the full published diagnostic criteria of growth deficiency; a full and characteristic set of minor facial anomalies including short palpebral fissures (more than two standard deviations from the mean), and a complex lower facial malformation sequence typified by flat philtrum, thin upper lip and apparent flattening of the midface just medial to the alae of the nose; and evidence of organic brain damage including structural, neurological, or functional stigmata. In these cases, there is clear evidence of exposure to alcohol during gestation by reliable report. Other malformations also may be found and are noted, but do not affect the final diagnosis.

FAS without a confirmed history of alcohol exposure. These patients have the same phenotypic findings as above, but no history of alcohol can be confirmed because the family of origin is not available, the birth records are sealed, or there is some similar situation. (We have never seen a patient with the full FAS phenotype and a confirmed negative history for alcohol exposure in gestation, but if such a patient would be found, they would not have FAS, but rather would be referred to as having an "FAS phenocopy.")

Atypical FAS. These patients have a phenotype that very nearly is complete for FAS and have a confirmed history of alcohol exposure. We place patients in this category when they have the full facial stigmata and brain changes of FAS, but lack growth deficiencies, or when they have growth deficiencies and brain changes of FAS, and most, but not all, of the facial anomalies. Specifically, they have short palpebral fissures and two out of three of the lower facial features, or all of the lower facial features and palpebral fissures that are more than one but less than two standard deviations from the mean. (In the past, we referred to this patient group as "possible FAS" or "partial FAS". Both of those terms proved problematic for patients, as we found that service providers interpreted "possible" FAS to mean an uncertain diagnosis and "partial" FAS to mean a milder form of the disorder.)

"Possible fetal alcohol effects" or "alcohol-related neurodevelopmental disorder." These terms both refer to a needed category(ies) for classifying patients exposed to alcohol in utero, but the terms themselves are less than ideal. The category broadly includes patients with some of the physical, cognitive, and/or behavioral problems that are among the problems seen in patients with FAS and an alcohol exposure history that would support high risk for alcohol teratogenesis. "Fetal alcohol effect" (FAE) was a term that was developed for research studies in humans or in animals when a teratogenic result (that was not full FAS) was clearly associated with alcohol exposure (Clarren & Smith, 1978). This term was needed because alcohol does have broad teratogenic impacts, especially on the brain, that are not necessarily related to obvious physical anomalies. The term "possible FAE" was proposed for clinical work as an entry on the differential diagnosis because the findings in these patients were generally nonspecific for alcohol teratogenesis and alcohol exposure could not be seen with certainty as the only cause. Although the term has been widely used by the public, it has been troubling or confusing to professionals who felt the term was used as a final diagnosis, rather than as a possible diagnosis, and that it overstated the established relationship between cause and effect (Aase, Jones, & Clarren, 1995). Further, what "effect" was being described? The term "alcohol-related birth defects" was proposed as an alternative (Sokol & Clarren, 1989). This term was not widely used because it did not seem to be appropriate to describe patients with functional brain dysfunction of probable organic origin as having a birth defect. Even more recently, the term "alcohol related neurodevelopmental disorder" has been suggested for this category name (Stratton, Howe, & Battaglia, 1996). The term is better in emphasizing the neurodevelopmental nature of the "effect," but this new term, in the end, continues to be problematic in its inherent link of etiology and outcome in the same phrase when the relationship between alcohol exposure and the likelihood of organic brain damage are each on a continuum from minimal to extreme, and the relationship between the two ranges from clinically very likely to clinically very unlikely. Better terminology is still needed and we are actively working on this problem at this time.

Financial Support

Much of the evaluation for FAS and related conditions, and most of the recommendations, are not medical, but rather social, educational, or involve mental health, so it is not wholly surprising that the costs are frequently not borne by medical insurers in total. We are finding that there are two ways to address this problem: build the

model within an existing system while avoiding duplication and develop multiple funding sources. Our clinic sites are establishing themselves within existing facilities in their communities such as public health departments, alcohol treatment facilities, and neurodevelopmental programs within a children's hospital. These organizations have pre-existing infrastructures that provide space, support systems, billing mechanisms, and natural linkages to other needed services. The development of various funding streams includes cash and in-kind contributions from private or government grants, fee-for-service contractual relationships for screening and diagnosing clients within a specific system (such as adoption agencies, schools, courts, and corrections), and support from managed care providers who do not wish to fully gear up to provide these diagnostic services themselves. In-kind support includes coverage of salaries for any of the clinic staff who serve the client population as part of their existing job (especially educational psychology, social work, and public health nursing). In-kind support also can include both professional and nonprofessional volunteers.

Results

In the first three years of clinic operation (January 8, 1993 to December 31, 1995), 1,839 requests were received for appointments to the FAS Diagnostic Clinic at the Center for Human Development and Disability. Of these, 816 families completed and returned the "New Patient Information Form," and 511 patients were evaluated. Among the 511 patients evaluated, 103 (20%) met the criteria for FAS (with or without confirmed exposure) or atypical FAS, and another 304 (60%) were placed in the FAE group. Males were more likely to have an FAS or FAE diagnosis. Sixty-six (64%) of FAS patients were male, and 168 (55%) of FAE patients were male (Table 1).

The racial background of the patients (Table 2) generally reflected the racial mix of Washington State, with the exceptions that patients with Native American ancestry were somewhat over-represented, and patients with Asian ancestry were under-represented.

Children with FAS and FAE generally did not live with their birth mothers (Table 2) . Only 15% of FAS patients and 21% of FAE patients lived with their birth mothers. The birth fathers or other family members cared for each group about 20% of the time. Fifty-five percent of the patients were in foster or adoptive care and 10% were living independently or in group homes. Few were incarcerated.

TABLE 1. Patient ages and gender by diagnosis.

Patient Diagnosis:	FAS (n = 103)	PFAE (n = 304)	Other (n = 104)	All (n = 511)
Age (yrs) at visit mean (s.d.) [min—max]	10.4 (7.5) [0.3—46.3]	10.2 (7.1) [0.6—50.9]	9.9 (8.6) [0.2—48.2]	10.2 (7.5) [0.2—50.9]
Gender M:F (% male)	66:37 (64)	168:136 (55)	54:50 (52)	266:223 (56)

TABLE 2. Selected patient characteristics by diagnosis.

Patient Diagnosis:	FAS (n = 103) n (%)	PFAE (n = 304) n (%)	Other (n = 104) n (%)	All (n = 511) n (%)
Race				
Caucasian	58 (56)	145 (48)	54 (52)	257 (50)
Black	9 (9)	29 (10)	10 (10)	48 (9)
Am/Alask Indian	21 (20)	79 (25)	19 (18)	119 (23)
Other	14 (14)	51 (17)	21 (20)	86 (17)
Unknown	1 (1)	0 (0)	0 (0)	1 (1)
Primary caretaker				
Birth mother	16 (15)	62 (21)	22 (21)	100 (20)
Birth father	8 (8)	27 (9)	6 (6)	41 (8)
Other family member	14 (13)	35 (12)	16 (15)	65 (13)
Foster care	28 (27)	99 (32)	28 (28)	155 (30)
Adoptive care	26 (26)	59 (20)	25 (24)	110 (22)
Other	10 (10)	22 (7)	7 (6)	38 (7)
Accompanied child to clinic				
Birth mother	17 (17)	72 (24)	28 (27)	117 (23)
Birth father	9 (9)	23 (8)	6 (6)	38 (7)
Other family member	9 (9)	37 (12)	12 (12)	58 (11)
Foster parent	31 (30)	86 (28)	24 (23)	141 (28)
Adoptive parent	26 (25)	59 (19)	24 (23)	109 (22)
Other	11 (10)	27 (9)	9 (9)	48 (9)

Approximately 90% of the patients paid for the assessment through Medicaid funding.

Although all of the patients had been assessed by at least one physician and many had seen numerous physicians and other professionals, the diagnosis of FAS had only been suggested in 4 of the 103 patients who met diagnostic criteria. Another 10 patients had been previously diagnosed as FAS but did not meet our diagnostic criteria.

Relatively few patients with FAS had medical problems that required follow-up. Nearly all needed coordinated services involving psychiatry (drug therapy for ADHD and/or mood), educa-

tional/vocational planning, behavioral therapy, family counseling and guidance, and drug and alcohol abuse counseling for older patients.

Discussion

Why is there a need for clinics uniquely devoted to patients with Fetal Alcohol Syndrome and related conditions? In part, the answer seems pragmatic. Our experience would suggest that the patients and their families do not seem to believe that their needs are met elsewhere. In part, the answer lies in the fact that the term "Fetal Alcohol Syndrome" actually identifies two patients. The "fetal alcohol" part of the term is relevant to etiology and is important in recognizing that the birth mother is a patient who is highly vulnerable to produce more affected children and to be judged as a poor caretaker of her current children. The diagnosis should direct us to her so that we can support her in her attempts at sobriety for her sake, and for the sake of her children and her unborn children. The "syndrome" part of the FAS term is relevant to the child who is likely to have complex cognitive and behavioral problems requiring the help of an appropriate team made up largely of educational and mental health professionals. Accurate diagnosis and treatment planning not only is needed for primary prevention and secondary disability prevention, but also is needed for epidemiological studies. Without accurate diagnosis and prevalence figures, the success of prevention programs cannot be gauged nor can appropriate budgets for intervention be calculated.

Our clinic model offers a comprehensive approach to the needs of both mothers and children. The clinic sites will be located conveniently throughout the state. Diagnosis will be consistent and defensible. Treatment planning will be comprehensive. In time, we can determine what services are available, or not available, available but not affordable, and effective or not effective. Clinics will aggressively, but sympathetically, reach out to birth mothers and help to identify factors that need to be addressed so that reductions in recurrent cases of FAS and FAE will occur. Finally, the clinics will be an important tool for surveillance programs.

If FAS screening is to be done, individuals who screen positive need to be evaluated for an accurate diagnosis and an appropriate treatment plan. Social groups and agencies in our state, including juvenile rehabilitation, foster care, and several Native American communities, already have approached the Network and asked to become clients of the system. Photographic screening of facial shape

(Stratton, Howe, & Battaglia, 1996) should be used to select the appropriate patients for clinical assessment.

The development of the FAS Diagnostic and Prevention Network is just underway. At this time, two of the FAS Diagnostic and Prevention Network sites are open and meeting once every other month, and four additional sites are in the training phase. The groups are all enthusiastic and committed. We are very optimistic that the program will be well-received within communities and will offer a much needed service.

Although the Washington State Legislature has only funded us to develop sites within Washington, the system could easily be expanded to a regional or national schema. This should be considered within a year or so, based on the success of the state-wide model.

End note: To obtain a copy of Astley and Clarren's manual, *Diagnostic Guide for Fetal Alcohol Syndrome and Related Conditions: The 4-Digit Diagnostic Code*, University of Washington, March 1997, contact: Fetal Alcohol Syndrome Diagnostic and Prevention Network, Children's Hospital and Medical Center, 4800 Sand Point Way N.E., CH-47, Seattle, WA 98105, or phone (206) 526-2206.

Cryptosporidiosis — Continued

To better understand the magnitude of cryptosporidiosis, health-care providers should specifically request testing for suspected cryptosporidiosis. Laboratories should consider routinely testing for *Cryptosporidium* as part of their ova and parasite examination protocol. Alternatively, when reporting test results back to health-care providers, laboratories should specifically indicate when *Cryptosporidium* is not tested for as part of a requested ova and parasite examination. Cryptosporidiosis is reportable in 41 states; interpretation of national data would be facilitated by mandatory reporting in all states.

Reference

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Child Health Month — October 1998

The American Academy of Pediatrics (AAP) has designated October as Child Health Month. This year, the AAP is focusing on the prevention of alcohol use and abuse that affects children and youth. Specific priorities include fetal alcohol syndrome (FAS), underage drinking, children of alcoholics, drinking and driving, and binge drinking.

Alcohol use during pregnancy has been cited as the most common known nongenetic cause of mental retardation among children and youth (*1*). Approximately 700 children aged 0–15 years die each year in alcohol-involved motor vehicle crashes; many of these children were being transported by a drunk driver (*2*). Approximately 80% of high school students have had at least one drink of alcohol, and one third have had five or more drinks on one or more occasions in any given month (*3*). During October, CDC, in collaboration with AAP and other organizations, will highlight the consequences of alcohol use as it relates to children and youth.

Additional information about Child Health Month is available from AAP, telephone (847) 981-7871, or the World-Wide Web, http://www.aap.org; and from the Health Resources and Services Administration, Maternal and Child Health Bureau, World-Wide Web, http://www.hhs.gov/hrsa/mchb. Information about FAS and other alcohol-related birth defects and developmental disabilities is available from CDC's Fetal Alcohol Syndrome Prevention Section, telephone (770) 488-7268, or the World-Wide Web, http://www.cdc.gov/nceh/programs/programs.htm. Information on the role of alcohol in traffic deaths among children and youth is available from CDC's National Center for Injury Prevention and Control, Division of Unintentional Injury Prevention, telephone (770) 488-4652, World-Wide Web, http://www.cdc.gov/ncipc/cmprfact.htm. Information on alcohol-related behaviors among youth is available from CDC's Division of Adolescent and School Health, telephone (770) 488-3168, World-Wide Web, http://www.cdc.gov/nccdphp/dash.

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Identification of Children with Fetal Alcohol Syndrome and Opportunity for Referral of their Mothers for Primary Prevention — Washington, 1993–1997

Heavy maternal use of alcohol during pregnancy can cause permanent birth defects, including fetal alcohol syndrome (FAS). Although these alcohol-related defects are entirely preventable, the factors associated with maternal use of alcohol during pregnancy are complex and often resistant to change. In addition, not all women who drink heavily will produce children with FAS (*1*). Although targeting primary prevention efforts to all women at risk for drinking during pregnancy is ideal, limited resources require targeting women at the highest risk for producing children affected by prenatal alcohol exposure. One such population is women who have already given birth to an alcohol-affected child (*2*). This high-risk population is not easily identified because not all children with FAS have their condition diagnosed, and these birth mothers are often separated from their children during the first few years of the child's life, often before a diagnosis of FAS has been considered. However, once identified, these women are receptive to intervention (*3*). To identify a population of women at highest risk for a future alcohol-exposed pregnancy through diagnosing a previously affected birth child, researchers at the University of Washington developed the Fetal Alcohol Syndrome Diagnostic and Prevention Network (FAS DPN). This report summarizes the results of this program and documents the feasibility of identifying persons who may have FAS so their condition can be diagnosed and their birth mothers can be identified and referred to prevention services.

FAS DPN opened its first clinical site at the Center for Human Development and Disability (University of Washington Medical Center, Seattle, Washington) in January 1993. Persons suspected of having FAS were identified through referral by various community sources and by directed screening of high-risk populations (*4*) (Table 1). Patients were then evaluated and their condition diagnosed in a multidisciplinary clinical setting (*5*), and birth mothers who were still at risk for producing additional affected children were identified, enabling referral to community alcohol treatment, family planning, and maternal advocacy programs (*6*).

During 1993–1997, there were 3002 requests for appointments for diagnostic evaluations at FAS DPN. To determine the appropriateness of referrals, parents and other caregivers were given a questionnaire (*7*) asking about the child's developmental and exposure history; 1374 completed the questionnaire. Persons referred for evaluation

TABLE 1. Number and percentage of patients referred to the Fetal Alcohol Syndrome (FAS) Diagnostic and Prevention Network, by referral source — Washington, 1993–1997*

Referral source	No.	(%)
Social services agencies†	334	(28.0)
Medical-care providers	267	(22.4)
Mental-health providers	184	(15.4)
FAS support organizations	147	(12.3)
Self referrals	124	(10.4)
School personnel	64	(5.4)
Lawyer or judge	23	(1.9)
Other	49	(4.1)

*Among the 1192 (87%) caregivers who responded to this question.
†Includes persons identified through photographic screening of high-risk populations.

Fetal Alcohol Syndrome — Continued

ranged from birth to middle age; the racial distribution was comparable to the general population in Washington, with a slight overrepresentation of American Indians. Approximately 20% lived with their birth mothers, 20% with other biological family members, and more than 50% with foster or adoptive parents. Although all patients had been seen in the health-care system before referral, only 56 of the 1374 caregivers completing the questionnaire reported that a diagnosis of FAS or related conditions had ever been considered and/or previously recorded in the medical or mental health records of the patient. Most diagnostic requests arose from concerns relating to issues of education and social skills (Table 2).

Because of limited capacity at the FAS DPN clinic, priority for diagnostic evaluation was based on responses to questions regarding in utero alcohol exposure and evidence of organic brain damage (based on previous medical and psychologic test results). Of the 1374 patients whose caregivers responded to the questionnaire, 811 were selected to receive diagnostic evaluations. Patients ranged in age from 0–51 years (mean: 10 years). Of these, 573 (71%) were found to have either documentation of in utero alcohol exposure or signs of organic brain damage; the remaining 238 had both. A total of 39 met the clinical criteria for an FAS diagnosis*, which includes elements of the FAS facial phenotype and growth deficiency in addition to in utero

*The FAS DPN uses a 4-Digit Diagnostic Code (*7*) that is consistent with the Institute of Medicine guidelines (*8*), but is a more detailed case definition.

TABLE 2. Number and percentage of reasons for referral to a fetal alcohol syndome (FAS) diagnostic and prevention clinic* — Washington, 1993–1997

Reason	No.	(%)
Problem with adaptation		
Conduct disorders, extreme anger	579	(45.8)
Poor judgement, cannot function independently	241	(19.1)
Poor self control, disorganized, unpredictable	238	(18.8)
Poor social skills	147	(11.6)
Poor parenting skills by patient	9	(0.7)
Problem with learning in school		
Learning disabilities, cognitive delays	400	(31.7)
Poor memory, does not learn from experience	117	(9.3)
Speech and language problems	99	(7.8)
Short attention span	360	(28.5)
Mental health concerns		
Depression, low self esteem	91	(7.2)
Medical concerns		
Face suggests a syndrome	138	(10.9)
Poor growth	40	(3.2)
Minor neurologic concerns	80	(6.3)
Physical or health concerns	122	(9.7)
Concerns about exposure		
Knowledge of alcohol exposure in utero	164	(13.0)
Ongoing drug/alcohol abuse by patient	31	(2.5)
Other		
Relation of possible FAS to a legal matter	32	(2.5)
Relation of possible FAS to placement	24	(1.9)
Patient with possible FAS is pregnant	1	(0.1)

*Among the 1260 (92%) caregivers who responded to this question. The caregiver could list more than one concern.

Fetal Alcohol Syndrome — Continued

alcohol exposure and organic brain damage. Only one of these 39 had FAS previously diagnosed.

The mothers of the 238 persons with both in utero alcohol exposure and signs of organic brain damage constitute a high-risk population for intervention to prevent subsequent affected offspring. Most (88%) of these women were aged ≤45 years (i.e., reproductive aged). Although only 51 (21%) birth mothers were living with the affected persons at the time of the diagnostic evaluation, the questionnaire provided sufficient information (i.e., name and location) for FAS DPN to identify 219 (92%) birth mothers.

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Editorial Note: This report documents one program's efforts to identify a population likely to have undiagnosed effects of in utero alcohol exposure. The birth mothers of these persons are a high-risk target population for primary prevention, although neither the mothers nor their health-care providers may realize their potential for producing subsequent affected children. The University of Washington is implementing a primary prevention intervention for these women that will rely on identification through early diagnosis of FAS in their children. For most patients in this study, an alcohol-related diagnosis had never been considered in any other medical or mental health setting, and only 22% were referred by a health-care care provider for further diagnostic services. This may be because the syndrome manifests itself in ways that may not be recognized in the traditional medical setting (*9*). As a result, multidisciplinary diagnostic clinics staffed by a physician, psychologist, language pathologist, occupational therapist, and social worker may facilitate the proper diagnosis of conditions in patients who have not been appropriately identified in other clinical settings.

The effectiveness of this approach relies on primary health-care providers being aware of the importance of diagnostic referral and on the availability of diagnostic resources. In 1993, the American Academy of Pediatrics (AAP) recommended increased awareness among pediatricians and health-care providers of FAS and other alcohol-related effects and the evaluation of children thought to have such conditions by a pediatrician skilled in the evaluation of neurodevelopmental and psychosocial problems (*10*). This report documents the need for continued efforts to implement these AAP recommendations, including forging stronger communication among parents and health-care providers about prenatal alcohol effects and providing or arranging access to skilled diagnostic assessment. This approach will increase the potential for primary prevention in avoiding subsequent exposures and will be a major protective factor in preventing secondary conditions among affected children (*9*).

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Fetal Alcohol Syndrome — Continued

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Notice to Readers

Availability of Continuing Medical Education Component in the *MMWR Recommendations and Reports* series, Vol. 47, No. RR-19

A Continuing Medical Education (CME) component is available in the paper and electronic versions of the October 16, 1998, *MMWR Recommendations and Reports* (Vol. 47, no. RR-19), *Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-Related Disease*. This component has been planned and implemented by CDC according to the Essentials and Standards of the Accreditation Council for Continuing Medical Education. CDC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CDC designates this educational activity for a maximum of 2.0 hours in category 1 credit toward the American Medical Association's Physician's Recognition Award. To register and to receive credit, physicians must return their responses either electronically to the World-Wide Web site http://www.cdc.gov/epo/mmwr/mmwr.html, then go to Continuing Education Program for Physicians and Nurses, or by a card or letter postmarked by October 16, 1999. There is no fee for participating in this CME activity. A CME component is planned for future *MMWR Recommendations and Reports*.

TERATOLOGY 59:163–172 (1999)

Fetal Alcohol Syndrome: Changes in Craniofacial Form With Age, Cognition, and Timing of Ethanol Exposure in the Macaque

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ABSTRACT One component of the fetal alcohol syndrome (FAS) facial phenotype is a frontonasal anomaly characterized by a thin upper lip and a smooth philtrum. The expression of this anomaly can diminish with age and occurs infrequently in prenatal alcohol-exposed individuals. This study sought to explain these observations. Standardized craniofacial cephalograms of 18 nonhuman primates exposed weekly to ethanol or sucrose solution in utero were measured at ages 1, 6, 12, and 24 months to assess skeletal changes in craniofacial form with age, cognition, and timing of ethanol exposure. The data suggest that there may be a critical period for induction of alcohol-induced craniofacial alterations that occurs very early in gestation and is very short in duration (gestational days 19 or 20). The alterations were scarcely detectable at age 1 month, were most prominent at 6 months, and diminished progressively at 12 and 24 months in the macaque. The appearance and disappearance of the thin upper lip and smooth philtrum may be explained by underlying changes in skeletal structure with age. The infrequent occurrence of the FAS frontonasal anomaly may be explained, in part, by its short critical period of induction. *Teratology 59:163–172, 1999.* © 1999 Wiley-Liss, Inc.

Fetal alcohol syndrome (FAS) is a permanent birth defect caused by maternal consumption of alcohol during pregnancy (Jones et al., '73, '74; Clarren and Smith, '78). Central nervous system dysfunction, growth deficiency, and a unique cluster of minor facial anomalies characterize FAS. Although FAS is a lifelong disability, the physical features are not always expressed throughout life.

The FAS facial phenotype is typified by small palpebral fissures and a complex lower frontonasal anomaly described by a thin upper lip and a smooth philtrum (Jones et al., '73; Astley and Clarren, '96). The philtrum is the area between the vermilion border of upper lip and subnasion. These frontonasal features are often, but not always, minimally expressed at birth, maximally expressed in childhood, and diminish again in adulthood. Although this variable presentation with age is documented anecdotally in the literature (Spohr et al., '87, '93; Streissguth et al., '91), there are no estimates as to how often these features change with age and there is little understanding of the morphological basis for this variation. The lip and philtrum are soft-tissue structures. One could speculate that the soft-tissue changes are secondary to changes in the underlying bony structures. Much like a smile can stretch a deeply grooved philtrum and thick upper lip into a smooth philtrum and thin upper lip (Fig. 1), so might underlying pressure from early overgrowth of the premaxilla.

Although the facial features are a key diagnostic component of the syndrome, they are minor anomalies, which are usually of little medical consequence to the individual. Of greater significance is the fact that the facial anomalies are midline anomalies derived from the anterior frontal neural crest primordia of the early forebrain. It has long been speculated that some midline facial anomalies are pathognomonic of brain malformation (i.e., the face predicts the brain) (DeMeyer, '75). This speculation is supported by the presence of a proportional increase in midventral forebrain deficiencies and the severity of facial dysmorphia in mice exposed to ethanol early in gestation (Sulik, '84). Earlier work by Sulik and Johnston ('82) also provided compelling evidence that the critical period for the induction of FAS-like craniofacial malformations occurs very early in gestation (gestational day 7 in the mouse, the primitive streak stage in embryogenesis) and is very short in duration (no more than a few hours in the

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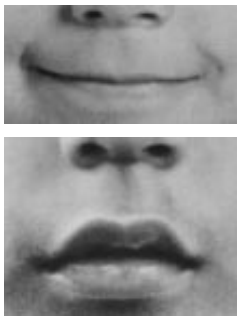

Fig. 1. Same individual with (**top**) and without (**bottom**) a smile, demonstrating how a smile can transform a deeply grooved philtrum (Likert rank = 2) (Astley and Clarren, '96) and full upper lip (Likert rank = 1, lip circularity [perimeter^2/area] = 40.9) (Astley and Clarren, '96) into a smooth philtrum (Likert rank = 4) and thin upper lip (Likert rank 5, lip circularity [perimeter^2/area] = 191.0).

mouse). Sulik and Johnston ('82) speculated that severe cases of FAS represent the mild end of the holoprosencephaly spectrum. Indeed, the only known nonhuman primate with holoprosencephaly was born after alcohol exposure in this project (Siebert et al., '91).

As form follows function, one could speculate that midline facial anomalies might also serve as markers for cognitive dysfunction. Although there is evidence to suggest that the magnitude of expression of the FAS facial phenotype is correlated with the severity of cognitive dysfunction (Jones et al., '73; Streissguth et al., '78; Streissguth and Dehaene, '93; Majewski, '81), these observations may be biased because the diagnostic criteria for FAS require the presence of both facial features and central nervous system (CNS) dysfunction.

An opportunity to assess variation in craniofacial form with timing of prenatal ethanol exposure, age, and cognitive dysfunction became available with the collection of standardized serial cephalometric radiographs of nonhuman primates (*Macaca nemestrina*) exposed to ethanol during gestation in a previous study (Clarren and Astley, '92; Clarren et al., '92). The primate model provides accurate documentation of timing and level of ethanol exposure, a controlled postnatal rearing environment, and a comprehensive battery of cognitive assessments, conditions which cannot be replicated in a human population (Clarren et al., '87, '88, '92; Clarren and Astley, '92; Astley et al., '95; Sirianni and Swindler, '85).

The present investigation was undertaken to address the following questions: 1) Does weekly prenatal ethanol exposure (1.8 g/kg maternal weight) result in detectable craniofacial malformations in *Macaca nemestrina* offspring? If malformations are detectable: 2) Is the primitive streak stage of embryogenesis a critical period of induction? 3) Does the magnitude of expression of alcohol-related craniofacial malformations change with age? 4) Is cognitive impairment correlated with the magnitude of craniofacial malformation?

MATERIALS AND METHODS

Subjects

A standardized series of cephalometric radiographs were collected at age 1, 6, 12, and 24 months on 18 nonhuman primates (*Macaca nemestrina*) who had been exposed to ethanol or a control solution of sucrose weekly during gestation (Clarren and Astley, '92) (Table 1).

Ethanol exposure

Details of timed-mating procedures, dosing schedules, and management of pregnancies were presented previously (Clarren and Astley, '92). Briefly, the animals were distributed across four exposure groups: 1) offspring exposed weekly to ethanol in the first 3 weeks of gestation, 2) offspring exposed weekly to ethanol in the first 6 weeks of gestation, 3) offspring exposed weekly to ethanol throughout the 24 weeks of gestation, and 4) a control group exposed weekly to sucrose solution, isocaloric and isovolemic to the ethanol dose, throughout gestation. To control for handling, dams in the 3- and 6-week ethanol groups received the sucrose solution weekly in all subsequent weeks of gestation.

Solutions were delivered to the dams via soft nasogastric tubes. All ethanol-exposed dams received ethanol at 1.8 g/kg maternal body weight, which resulted in mean peak plasma ethanol concentrations of 223 $\pm$ 28 mg/dl. These weekly dosing schedules were established to mimic the most common pattern of female drinking, i.e., weekend social drinking which often stops upon confirmation of pregnancy.

Cephalograms

Standardized lateral and frontal cephalograms of each offspring were obtained with the sedated animal seated in a cephalostat designed for nonhuman primate cephalometry (Sirianni and Swindler, '85). Kodak X-Omat TL industrial, high-resolution film was used. The X-ray beam was centered along the Frankfort horizontal plane for both the lateral and frontal cephalograms with a tube-film distance of 49 cm and a subject-film distance of 14 cm. Cephalograms were taken at age 1, 6, 12, and 24 months. This age distribution is approximately equivalent to age 4 months, 2 years, 4–6 years, and 8–10 years in the human.

Each frontal and lateral cephalogram was captured at 640 $\times$ 480 pixel resolution on a 256-unit gray scale using Optimas image acquisition and enhancement computer software (Optimas Corp., Edmonds, WA). The software was used to mark and derive the X, Y Cartesian coordinates of 19 standardized skeletal landmarks (Fig. 2). Basion could not be reliably identified in the cephalograms at age 1 month. A cleared skull with lead-marked landmarks was radiographed to serve as a guide for landmark identification. The X, Y coordinates

TABLE 1. Selected characteristics of study population (18 *Macaca nemestrina*)

Offspring ID no.		Ethanol-exposed on gestational days 19 or 20	Weeks of ethanol exposure*	Cognitive impairment score**	Gender	Postnatal age (months) at X-ray, postconceptional age (days)			
No.	Eartag					1	6	12	24
45	CF	Yes	3	8	M	212	351	539	910
49	RG	Yes	6	67	F	198	351	532	917
50	SA	Yes	6	33	M	203	351	532	909
56	SI	Yes	24	18	F	196	350	533	897
40	DX	No	0	0	F	199	354	535	900
34	LP	No	0	10	F	197	352	554	962
35	OH	No	0	10	F	199	352	543	899
36	SB	No	0	0	F	205	353	539	914
38	TU	No	0	0	F	200	354	539	902
39	VO	No	0	8	F	200	354	536	906
41	NT	No	3	20	M	198	354	537	902
43	XF	No	3	8	F	201	354	548	914
44	AE	No	3	8	M	204	351	534	918
46	ER	No	3	33	F	197	363	534	904
48	KX	No	6	20	F	200	354	537	984
51	SC	No	6	8	M	197	352	538	906
52	SR	No	6	25	F	199	352	534	911
55	SH	No	24	33	M	201	355	538	902

*Weekly ethanol exposure for first 3, 6, or 24 weeks of gestation. Maternal dose, 1.8 g/kg ethanol.
**Represents percent of cognitive and behavioral tests failed (Clarren and Astley, '92).

of the landmarks were used to calculate 17 linear and 3 angular measurements (Table 2). These measures were selected to best capture the craniofacial form associated with FAS. Head circumference (OFC) and body weight were measured at the time of each X-ray. Brain weight and volume were recorded at the time of sacrifice (age 4.0–5.3 years).

Cognitive assessments

Motor, cognitive, behavioral, and physical development was documented from birth through age 14 months. The comprehensive assessment battery was developed and has been administered at the Infant Primate Research Laboratory for over 20 years. The content and timing of the assessments are described in detail in previous reports (Clarren et al., '88, '92). An unweighted composite score reflecting each animal's developmental impairment was derived by dividing the number of assessments an animal failed by the number of assessments used to summarize each animal's development in Figure 1 as presented in Clarren et al. ('92). Failure for each assessment was defined as performance >2 SDs below the mean performance of the control animals.

Analysis

Repeated-measures analysis of covariance, with adjustment for gender, was used to compare mean distance and angular craniofacial measures between the ethanol-exposed and unexposed groups at age 1, 6, 12, and 24 months. To evaluate the impact of timing of exposure on outcome, the analysis was repeated three times with the animals' exposure status classified in three different ways: 1) in their original four groups based on *duration* of exposure (0, 3, 6, or 24 weeks), 2) in two groups based on *exposed / not exposed* (the 3-, 6-, and 24-week groups were combined and compared to the control group), and 3) in two groups based on *exposed or not exposed on gestational days 19 or 20*. The rationale for these three different exposure classifications is as follows. Facial development is essentially complete by the seventh week of gestation in the macaque, with a potential critical period of vulnerability occurring as early as week 3 (Sulik and Johnston, '83). Since all ethanol-exposed animals started their weekly exposures within the first 13 days of gestation, we hypothesized that classifying the animals by duration of exposure would be least sensitive for identifying craniofacial contrasts, classifying them based on exposed/not exposed would be more sensitive, and that classifying them based on who received ethanol exposure specifically on gestational days 19 or 20 would be the most sensitive. Gestational days 19 and 20 in the macaque correspond with the critical period of induction for FAS facial malformations (gestational day 7 or the primitive streak stage) observed in the mouse (Sulik and Johnston, '83).

Multiple linear regression analyses with adjustment for gender were conducted to detect correlations between craniofacial measures and the overall cognitive impairment score. These analyses were repeated at each of the four ages (1, 6, 12, and 24 months).

It is important to note that the original primate study from which these data were derived was not designed to address the specific questions presented in this study. Due to the small number of animals in each exposure group, only large contrasts between groups were statistically detectable. In general, when a study's power to detect a clinically meaningful contrast drops below 80%, the study is at risk for falsely declaring an absence

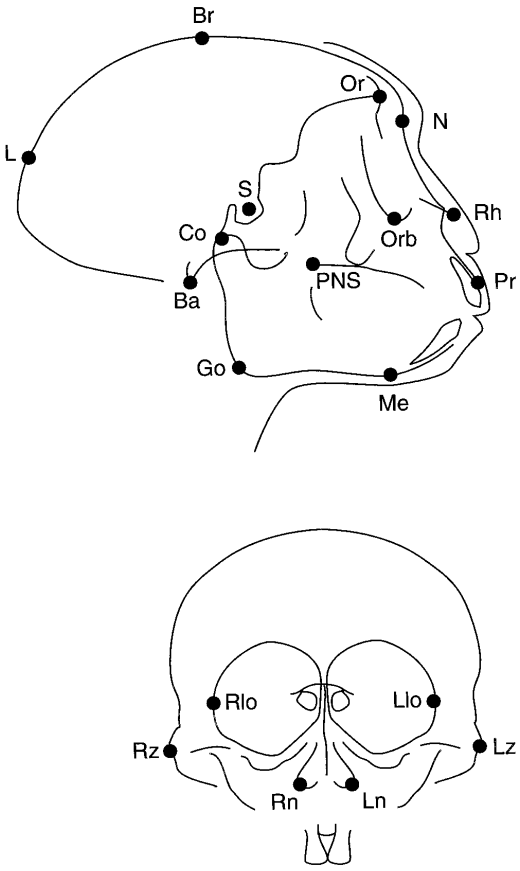

Fig. 2. Landmarks on lateral radiographs. L, lambda, most superior point on the lambdoid suture; Br, bregma, point at junction of coronal and sagittal sutures; S, sella, center of pituitary fossa of the sphenoid bone; Go, gonion, midpoint of angle of mandible; PNS, posterior nasal spine, most posterior point at the sagittal plane on the bony hard palate; Co, condylion, most posterior, superior point on curvature on average of right and left outlines of condylar heads; Ba, basion, most inferior, posterior point on anterior margin of foramen magnum; Or, junction of orbital roof and inner table of the frontal bone; Orb, orbitale, lowest point on average of right and left borders on the bony orbit; Me, menton, most inferior point on the symphyseal outline; N, nasion, junction of frontonasal suture at the deepest point on curve at bridge of nose; Rh, rhinion, most superior, inferior point of nasal bone; Pr, prosthion, most anteroinferior point on upper alveolar margin. Landmarks on frontal radiographs. Rlo, right lateral orbit, at point where zygomatic and frontal bones meet; Llo, left lateral orbit, at point where zygomatic and frontal bones meet; Rz, right zygoma, most lateral portion of zygomatic arch; Lz, left zygoma, most lateral portion of zygomatic arch; Rn, right nasal cavity, most lateral portion of nasal cavity; Ln, left nasal cavity, most lateral portion of nasal cavity.

of contrast between groups. When between-group contrasts observed in this study failed to achieve statistical significance, these outcomes were accompanied by estimates of the minimum effect sizes that could have been detected at 80% power (Bornstein et al., '97).

TABLE 2. Morphometric measurements*

Lateral cephalometric films	
Cranial measurements	
Cranial height	Ba-Br
Anterior cranial base	S-Or
Posterior cranial base	S-Ba
Posterior cranium	S-L
Cranial vault height	S-Br
Cranial length	L-Or
Cranial base angle	Ba-S-Or
Sagittal cranial area (at midline)	L-S-Or-Br
Midface measurements	
Midface height	N-Pr
Posterior midface height	S-PNS
Facial depth I	S-Rh
Facial depth II	S-Orb
Facial depth III	S-Pr
Palatal length	PNS-Pr
Facial angle	Or-Pr-PNS
Anterior cranial base to facial plane	S-Or-Pr
Mandibular measurements	
Mandibular body length	Go-Me
Mandibular ramus height	Go-Co
Frontal cephalometric films	
Interorbital width	Rlo-Llo
Bizygomatic width	Rz-Lz
Nasal cavity width	Rn-Ln

*Abbreviations used are spelled out in Figure 2.

Measurement precision

Landmark identification was repeated, 2 weeks apart, on 10 randomly selected cephalograms. The measurements for each set of radiographs were compared and revealed a high degree of precision. The method error was determined by the equation of Dahlberg ('40), where the sum of the squared differences is divided by two times the number of measurements and the square root is calculated. The method error was 0.27 mm for linear and 1° for angular measurements. Error calculated as a percentage of the measurements examined was less than 2%.

RESULTS

Effect of ethanol exposure and age on craniofacial form

When the cephalometric measurements were compared between the 0-week (n = 6), 3-week (n = 5), 6-week (n = 5), and 24-week (n = 2) ethanol exposure groups to test whether craniofacial form and brain size varied as the duration of exposure increased, only one statistically significant trend was detected. At age 6 months, mean cranial length (L-Or) increased linearly from 71.4 mm to 73.9 mm to 75.1 mm to 76.7 mm as duration of exposure increased from 0 to 3 to 6 to 24 weeks, respectively ($P = 0.03$). It is worth noting that the same pattern and relative magnitude of change in cranial length were also observed at ages 1, 12, and 24 months. Increased variability in cranial length dropped the power of detection to less than 35%, which may explain why these trends failed to achieve statistical significance. Mean head circumference was comparable (maximum contrast 5%) between all four groups across

all ages. Mean brain weight and volume were comparable (maximum contrast 10%) between all four groups at sacrifice. This series of analyses had 80% power to detect a ≥2 mm (or 5%) and a ≥2° (or 10%) incremental change in linear and angular craniofacial measures, a ≥9 mm (or 4%) incremental change in OFC, and an ≥8 g or cc (or 10%) incremental change in brain weight or volume.

When the analyses were repeated with the animals reclassified as exposed (n = 12) and not exposed (n = 6) to ethanol, again, only a few contrasts in craniofacial form were detected. All linear measures at each of the four ages were consistently greater in the ethanol-exposed animals relative to the unexposed animals. On average, the 20 linear measures were 3.5 ± 4.9% greater at age 1 month, 4.5 ± 3.1% greater at age 6 months, 2.2 ± 2.3% greater at age 12 months, and 2.5 ± 2.6% greater at age 24 months in the ethanol-exposed animals relative to the nonexposed animals. There was no consistent pattern or direction of change in the three angular measures across the four ages. The only contrasts which achieved statistical significance included an increased orbital distance (Rlo-Llo) by 1.7 mm (or 4%) at ages 6 and 24 months ($P = 0.01$), and an increased cranial length (L-Or) by 3.5 mm (or 5%) at age 6 months ($P = 0.04$) in the ethanol exposed animals relative to the unexposed animals. Mean head circumference was comparable (2–4% difference) between the exposed and unexposed groups across all ages. Mean brain weight and volume were comparable (3% difference) across the two groups at sacrifice. These analyses had an estimated 80% power to detect a ≥3 mm or degree (or 5–10%) difference between the craniofacial measures, a ≥15 mm (or 6%) difference in OFC, and a ≥15 g or cc (or 20%) difference in brain weight or volume between the two exposure groups.

When the analyses were repeated one more time with the animals reclassified as exposed (n = 4) or not exposed (n = 14) to ethanol on gestational days 19 or 20 (the period comparable to gestational day 7 in the mouse found to be important by Sulik and Johnston, '82), substantially more contrasts were identified (Table 3, Fig. 3). On average, the 20 linear measures were 2.8 ± 3.8% greater at age 1 month, 4.8 ± 5.1% greater at age 6 months, 3.2 ± 3.7% greater at age 12 months, and 5.4 ± 1.9% greater at age 24 months in the animals exposed on days 19 or 20 relative to those not exposed on days 19 or 20. On average, the three angular measures were 0.1 ± 2.6% smaller at age 1 month, 4.6 ± 3.0% smaller at age 6 months, 1.1 ± 1.3% smaller at age 12 months, and 0.3 ± 1.4% smaller at age 24 months in the animals exposed on days 19 or 20 relative to those not exposed on days 19 or 20. The number of statistically significant contrasts in craniofacial form between the two groups of animals was minimal at age 1 month, increased substantially at age 6 months, and diminished again at age 12 and 24 months. More specifically, at age 1 month, only 3 of the 20 craniofacial measures were significantly different in the animals exposed on days 19 or 20: head length (L-Or) was 3.7 mm (or 5.5%) greater, OFC was 8.0 mm (or 3.7%) greater, and facial depth (S-Pr) was 2 mm (or 5.7%) greater. At age 6 months, 6 of the 20 measures were significantly different in the animals exposed on days 19 or 20. These included head length (L-Or) greater by 4.2 mm (or 5.8%), midface height (N-Pr) greater by 4.5 mm (or 17.6%), two measures of facial depth (S-Rh greater by 4 mm (or 11%), and S-Pr greater by 2.7 mm (or 6.3%), facial angle (Or-Pr-PNS) smaller by 4.7° (or 7.9%), and internasal width (Rn-Ln) greater by 1.5 mm (or 14.9%). At age 12 months, 3 of 20 measures were significantly greater in the animals exposed on days 19 or 20: cranial length (L-Or) by 4.4 mm (or 5.9%), posterior midface height (S-PNS) by 1.8 mm (or 10.6%), and internasal width (Rn-Ln) by 1.1 mm (or 10.3%). At age 24 months, 4 of the 20 measures were significantly different between the animals exposed and not exposed to ethanol on gestational days 19 or 20. These included cranial length (L-Or) greater by 5.8 mm (or 7.8%), OFC greater by 15.3 mm (or 5.9%), interorbital width (Rlo-Llo) greater by 1.4 mm (or 2.8%), and bizygomatic width (Rz-Lz) greater by 3.1 mm (or 7.3%). The mean brain weight in grams was 94.9 ± 6.3 vs. 84.8 ± 8.8 ($f = 3.2$, $P = 0.11$) in the animals exposed and not exposed to ethanol on gestational days 19 or 20, respectively. The mean brain volume in cubic centimeters was 88.0 ± 5.3 vs. 80.1 ± 8.1 ($f = 2.3$, $P = 0.16$) in the animals exposed and not exposed to ethanol on gestational days 19 or 20, respectively. This series of analyses had 80% power to detect a ≥3 mm (or 5%) or ≥3 degree (or 10%) difference between craniofacial measures, a ≥15 mm (or 5%) difference in OFC, and a ≥15 g or cc (or 20%) difference in brain weight or volume between the two exposure groups.

As further evidence that the critical period of induction may be gestational days 19 or 20 in the macaque, two additional exploratory analyses were conducted, comparing all craniofacial measures between animals exposed and not exposed to ethanol just prior to the critical period (gestational days 17 or 18) and comparing animals exposed and not exposed to ethanol just after the critical period (gestational days 21 or 22). No statistically significant contrasts were identified in either analysis.

Correlations between craniofacial form and cognition

The cognitive impairment score increased as craniofacial linear measures increased and craniofacial angular measures decreased (Table 4, Fig. 4). The directions of these correlations were consistent with the alcohol-related changes observed in the animals exposed to ethanol on gestational days 19 or 20. The proportion of craniofacial measures that correlated significantly with cognitive impairment increased with age: 12% at age 1 month, 21% at age 6 months, 37% at age 12 months, and 32% at age 24 months. The magnitude of the correlations also increased with age. At age 12 months, when the greatest number of correlations was observed, cognitive impairment increased significantly with in-

TABLE 3. Craniofacial contrasts between 4 animals that did and 14 animals that did not receive ethanol exposure on gestational days 19 or 20 (primitive streak stage or Carnegie stage 9)*

		Postnatal age											
		1 month			6 months			12 months			24 months		
Craniofacial measure	Group	Mean	(SD)	*P*	Mean	(SD)	*P*	Mean	(SD)	*P*	Mean	(SD)	*P*
Cranial height (mm) Ba-Br	Control	Insufficient data			46.1	(1.4)	0.84	48.0	(1.7)	0.96	49.5	(2.3)	0.17
	Ethanol				46.4	(1.5)		48.0	(1.2)		51.5	(1.2)	
Anterior cranial base (mm) S-OR	Control	27.8	(1.0)	0.12	32.4	(1.7)	0.33	34.0	(1.4)	0.18	35.2	(1.7)	0.07
	Ethanol	28.9	(1.0)		33.6	(1.1)		35.3	(1.1)		37.1	(1.0)	
Posterior cranial base (mm) S-Ba	Control	Insufficient data			15.8	(1.1)	0.93	16.9	(0.9)	0.74	17.8	(1.1)	0.12
	Ethanol				15.9	(0.9)		17.0	(0.8)		18.8	(0.7)	
Posterior cranium (mm) S-L	Control	44.6	(1.6)	0.31	46.7	(1.7)	0.15	47.0	(1.7)	0.08	47.7	(2.0)	0.09
	Ethanol	45.7	(0.8)		48.2	(1.0)		48.7	(0.8)		49.8	(0.9)	
Cranial vault height (mm) S-Br	Control	32.8	(1.5)	0.60	35.8	(1.9)	0.63	36.5	(1.8)	0.89	37.9	(2.1)	0.56
	Ethanol	32.7	(2.1)		35.7	(2.0)		36.9	(1.4)		38.8	(2.3)	
Cranial length (mm) L-Or	Control	67.7	(2.1)	0.009	72.8	(2.6)	0.02	73.6	(2.0)	0.003	74.2	(2.8)	0.004
	Ethanol	71.4	(1.2)		77.0	(1.9)		78.0	(2.4)		80.0	(1.9)	
Cranial base angle (°) Ba-S-Or	Control	Insufficient data			166.5	(5.6)	0.05	166.8	(5.6)	0.41	170.6	(4.5)	0.43
	Ethanol				159.4	(7.1)		163.9	(4.5)		168.1	(4.9)	
Anterior cranial base to facial plane (°) S-Or-Pr	Control	79.3	(1.8)	0.09	80.6	(2.7)	0.21	83.1	(2.7)	0.86	84.3	(2.4)	0.50
	Ethanol	81.7	(3.4)		78.8	(5.0)		83.4	(2.9)		85.4	(3.2)	
Head circumference (mm)	Control	215.8	(6.3)	0.04	237.1	(7.9)	0.20	249.6	(9.2)	0.26	259.7	(8.8)	0.02
	Ethanol	223.8	(4.8)		243.8	(6.9)		256.5	(10.1)		275.0	(11.2)	
Midface height (mm) N-Pr	Control	22.1	(1.5)	0.74	25.5	(1.9)	0.005	28.3	(2.2)	0.44	36.1	(3.3)	0.36
	Ethanol	22.6	(0.5)		30.0	(2.9)		29.5	(5.4)		38.5	(5.9)	
Posterior midface height (mm) S-PNS	Control	11.4	(0.7)	0.07	15.9	(1.4)	0.21	17.0	(1.0)	0.04	19.5	(1.3)	0.10
	Ethanol	12.5	(1.4)		17.1	(1.8)		18.8	(2.1)		21.1	(2.1)	
Facial depth I (mm) S-Rh	Control	31.4	(1.3)	0.06	36.5	(1.5)	0.001	39.9	(1.3)	0.08	44.8	(2.0)	0.07
	Ethanol	33.2	(2.0)		40.5	(1.6)		42.2	(3.7)		47.8	(3.9)	
Facial depth II (mm) S-Orb	Control	23.1	(1.8)	0.11	28.5	(1.2)	0.72	30.0	(0.9)	0.12	32.3	(2.0)	0.34
	Ethanol	25.0	(1.4)		28.8	(0.5)		31.0	(1.1)		33.6	(0.9)	
Facial depth III (mm) S-Pr	Control	35.0	(1.4)	0.046	42.8	(1.8)	0.02	47.8	(1.4)	0.09	55.2	(2.9)	0.14
	Ethanol	37.0	(1.9)		45.5	(1.3)		50.0	(3.2)		58.1	(3.4)	
Palatal length (mm) PNS-Pr	Control	24.9	(1.2)	0.47	28.5	(1.5)	0.30	32.6	(1.3)	0.99	37.3	(2.2)	0.36
	Ethanol	25.6	(0.9)		29.4	(1.4)		32.5	(2.2)		38.4	(1.2)	
Mandibular body length (mm) Go-Me	Control	22.1	(1.4)	0.55	26.4	(1.9)	0.59	29.5	(1.4)	0.05	34.8	(3.0)	0.18
	Ethanol	22.7	(0.6)		27.3	(0.6)		31.2	(0.6)		37.0	(0.8)	
Mandibular ramus height (mm) Go-Co	Control	Insufficient data			20.7	(1.8)	0.68	24.5	(1.7)	0.53	27.0	(2.7)	0.18
	Ethanol				21.2	(1.3)		23.2	(1.5)		28.3	(2.0)	
Facial angle (°) Or-Pr-PNS	Control	61.8	(2.1)	0.39	59.6	(2.7)	0.007	56.1	(3.0)	0.45	49.0	(2.4)	0.79
	Ethanol	60.6	(3.4)		54.9	(5.4)		54.9	(5.4)		48.7	(5.6)	
Interorbital width (mm) Rlo-Llo	Control	39.9	(1.5)	0.38	44.5	(1.3)	0.14	47.1	(0.8)	0.16	50.6	(1.2)	0.03
	Ethanol	40.6	(1.0)		45.3	(0.5)		47.8	(1.1)		52.0	(0.8)	
Bizygomatic width (mm) Rz-Lz	Control	49.0	(2.4)	0.33	59.1	(2.2)	0.19	63.6	(2.1)	0.13	69.7	(2.3)	0.03
	Ethanol	50.2	(1.9)		60.5	(1.3)		65.4	(1.8)		72.8	(2.0)	
Internasal width (mm) Rn-Ln	Control	8.8	(1.5)	0.43	10.1	(1.2)	0.04	10.7	(1.1)	0.049	12.2	(1.0)	0.10
	Ethanol	8.1	(2.0)		11.6	(1.2)		11.8	(0.7)		13.3	(1.2)	

*SD, Standard deviation; *P*, repeated measures analysis of variance two-tailed *P* value after adjustment for gender. Craniofacial measure abbreviations are spelled out in Fig 2. Statistically significant outcomes are underlined.

creasing cranial length (L-Or), increasing posterior midface height (S-PNS), increasing facial depth (S-Rh, S-Orb, S-Pr), and decreasing facial angle (Or-Pr-PNS).

DISCUSSION

This investigation of craniofacial morphology in *Macaca nemestrina* exposed to ethanol in utero revealed significant craniofacial alterations and substantiates previous reports of teratogenesis with weekly 1.8 g/kg gestational ethanol exposure in nonhuman primates (Clarren et al., '88, '92). To achieve the maternal peak plasma ethanol levels recorded for this sample of nonhuman primates, the average woman would need to consume 6–9 beers in the course of a few hours. In brief summary, the results of this study suggest that there may be a critical period for induction of alcohol-induced craniofacial alterations that occurs very early in the macaque's gestation and is very short in duration (gestational days 19 or 20). The ethanol-induced craniofacial alterations were scarcely detectable at age 1 month, were most prominent at age 6 months, and diminished progressively at ages 12 and 24 months.

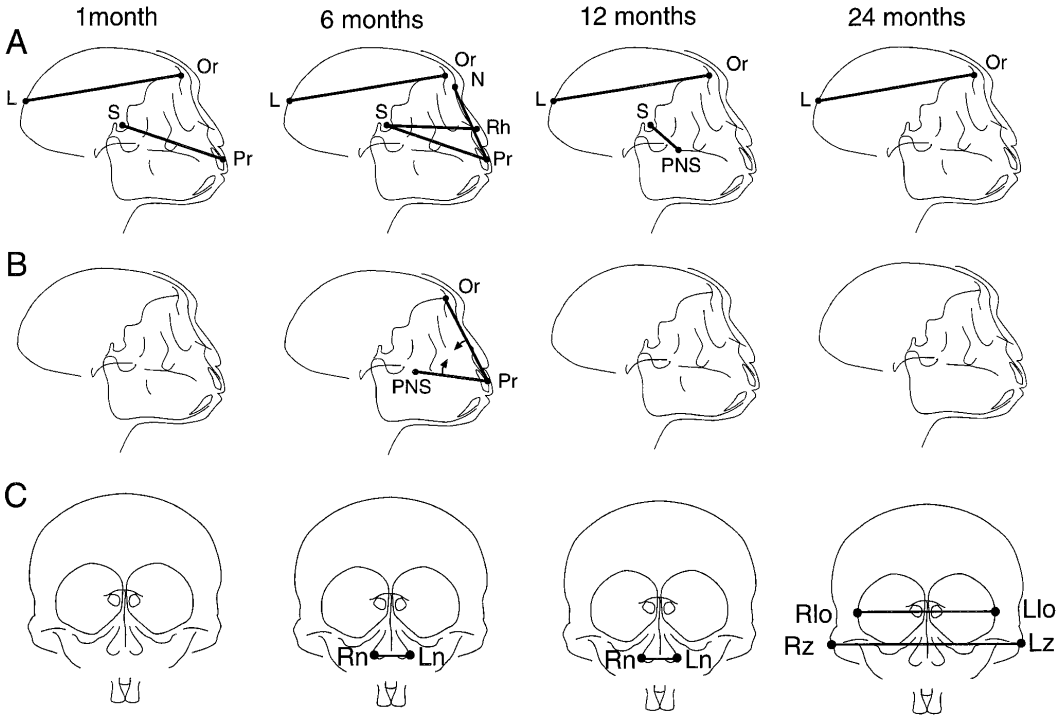

Fig. 3. Overview of craniofacial contrasts at age 1, 6, 12, and 24 months among 4 animals exposed to ethanol on gestational days 19 or 20 relative to 14 animals not exposed on gestational days 19 and 20. **A, C:** Straight lines reflect dimensions that were significantly greater at the $P < 0.05$ level in the 4 animals exposed on gestational days 19 or 20. **B:** The angular measure was significantly smaller in the 4 animals exposed on gestational days 19 or 20. Same abbreviations as in Figure 2.

Finally, the strong correlations observed between alcohol-induced craniofacial alterations and cognitive impairment suggest that midline facial anomalies may be sensitive indicators of brain dysfunction.

Timing of ethanol exposure

As we hypothesized, classifying the animals based on who did or did not receive ethanol exposure on gestational days 19 or 20 resulted in the maximum number of craniofacial contrasts, supporting Sulik ('84), who found that the critical period of induction for FAS-like facial anomalies occurred very early in gestation (gestational day 7 in the mouse, the primitive streak stage) and was very short in duration (just a few hours in the mouse). The findings from these two studies may explain, in part, why only an estimated 1–9% of women who are chronic alcoholics give birth to a child with FAS (Abel and Sokol, '87). A diagnosis of FAS requires the presence of the FAS facial phenotype. If the critical period of induction for the FAS facial phenotype is truly only 1 or 2 days long, even a frequent drinker could fail to expose her fetus on those days.

Sulik and Johnston ('82) also demonstrated that ethanol can induce holoprosencephaly in a mouse model, supporting the speculation that severe cases of FAS represent the mild end of holoprosencephaly. Interestingly, the only documented case of holoprosencephaly in a nonhuman primate occurred in this study, in an animal whose weekly ethanol exposure included exposure on gestational day 19 (Siebert et al., '91).

Craniofacial form and changes with age

The macaques exposed to ethanol on gestational days 19 or 20 had significantly longer midfaces (N-Pr) and protruded premaxillas (S-Rh, S-Pr, and S-PNS). These craniofacial alterations were barely detectable at age 1 month, were most strongly expressed at age 6 months, and progressively diminished at ages 12 and 24 months. These results are not only consistent with observations in the human population (Fig. 1), but may also explain why the soft-tissue anomalies associated with the FAS facial phenotype vary with age. It has long been our belief that the appearance and disappearance of the smooth philtrum and thin upper lip in individuals with

TABLE 4. Correlations between craniofacial measures over time with cognitive impairment score*

Craniofacial measure	Group	Postnatal age: 1 month Corr.	1 month R^2	1 month *P*	6 months Corr.	6 months R^2	6 months *P*	12 months Corr.	12 months R^2	12 months *P*	24 months Corr.	24 months R^2	24 months *P*
Cranial height (mm) Ba-Br	Control	Insufficient data			(−.25)	.60	0.35	(−.10)	0	0.71	(−.07)	.01	0.77
	Ethanol												
Anterior cranial base (mm) S-OR	Control	(−.15)	.02	0.54	(+.11)	.01	0.67	(+.10)	0	0.71	(+.09)	0	0.75
	Ethanol												
Posterior cranial base (mm) S-Ba	Control	Insufficient data			(−.29)	.08	0.28	(+.19)	.04	0.44	(+.19)	.03	0.46
	Ethanol												
Posterior cranium (mm) S-L	Control	(+.03)	0	0.96	(+.37)	.14	0.13	(+.36)	.13	0.14	(+.16)	.03	0.52
	Ethanol												
Cranial vault height (mm) S-Br	Control	(−.47)	.22	0.05	(−.34)	.11	0.18	(−.26)	.07	0.31	(−.25)	.07	0.31
	Ethanol												
Cranial length (mm) L-Or	Control	(+.31)		0.22	(+.54)	.30	0.02	(+63)	.40	0.005	(+.44)	.21	0.07
	Ethanol												
Cranial base angle (°) Ba-S-Or	Control	Insufficient data			(−.62)	.38	0.01	(−.36)	.13	0.15	(−.51)	.27	0.03
	Ethanol												
Anterior cranial base to facial plane (°) S-Or-Pr	Control	(+.58)	.34	0.01	(+.09)	0	0.73	(0)	0	0.99	(−.09)	0	0.99
	Ethanol												
Head circumference (mm)	Control	(+.07)	0	0.19	(+.19)	.03	0.46	(+.28)	.08	0.28	(+.41)	.17	0.10
	Ethanol												
Midface height (mm) N-Pr	Control	(−.15)	.02	0.56	(+.26)	.07	0.30	(+.48)	.23	0.04	(+.50)	.25	0.04
	Ethanol												
Posterior midface height (mm) S-PNS	Control	(+.37)	.14	0.13	(+.32)	.10	0.20	(+.46)	.21	0.057	(+.55)	.30	0.02
	Ethanol												
Facial depth I (mm) S-Rh	Control	(+.17)	.03	0.51	(+.43)	.18	0.08	(+.61)	.37	0.008	(+.58)	.33	0.01
	Ethanol												
Facial depth II (mm) S-Orb	Control	(+.19)	.04	0.47	(+.29)	.09	0.24	(+.53)	.28	0.03	(+.27)	.07	0.28
	Ethanol												
Facial depth III (mm) S-Pr	Control	(+.20)	.04	0.43	(+.46)	.21	0.055	(+.61)	.37	0.007	(+.45)	.20	0.06
	Ethanol												
Palatal length (mm) PNS-Pr	Control	(−.04)	.01	0.84	(+.22)	.05	0.39	(+.30)	.09	0.23	(+.17)	.03	0.50
	Ethanol												
Mandibular body length (mm) Go-Me	Control	(+.21)	.04	0.41	(+.32)	.10	0.20	(+.41)	.17	0.09	(+.24)	.06	0.34
	Ethanol												
Mandibular ramus (mm) Go-Co	Control	Insufficient data			(−.15)	.02	0.57	(−.11)	.10	0.65	(+.07)	0	0.79
	Ethanol												
Facial angle (°) Or-Pr-PNS	Control	(−.31)	.09	0.22	(−.34)	.12	0.16	(−.47)	.22	0.05	(−.48)	.23	0.04
	Ethanol												
Interorbital width (mm) Rlo-Llo	Control	(−.21)	.04	0.41	(+.21)	.03	0.45	(+.22)	.05	0.40	(+.36)	.08	0.14
	Ethanol												
Bizygomatic width (mm) Rz-Lz	Control	(−.25)	.06	0.31	(+.11)	.01	0.70	(+.28)	.08	0.27	(+.40)	.11	0.10
	Ethanol												
Internasal width (mm) Rn-Ln	Control	(−.42)	.18	0.08	(+.49)	.24	0.055	(+.45)	.20	0.07	(+.51)	.26	0.03
	Ethanol												

*Corr., Pearson correlation coefficient; R^2, proportion of variance in cognitive impairment score explained by craniofacial measure after adjustment for gender. Reported only when stepwise selection process in the multiple linear regression included craniofacial measure in the model. *P*, *P*-value for craniofacial measure partial correlation coefficient, if craniofacial measure was included in the model. Abbreviations for column 1 are spelled out in Fig 2. Statistically significant outcomes are underlined.

FAS may be secondary to alterations in underlying bony structure with age. Just as a smile can stretch a deeply grooved philtrum and full upper lip into a smooth philtrum and thin upper lip (Fig. 1), protrusion of the premaxilla could have a similar effect. The timing of the onset and regression of the premaxillary protrusion observed in this study closely corresponds with the timing of the appearance and disappearance of smooth philtrums and thin upper lips observed in the human population. It is interesting to note that Martin et al. ('96) identified distinct differences in the structure of the upper lip in a study comparing philtral development in the normal fetus with philtral development in specimens (including a specimen with prenatal alcohol exposure) lacking normal philtral landmarks. These findings, however, do not readily explain why philtrum smoothness varies with age. These contrasts in philtral muscular structure may explain the degree to which philtrums and upper lips are malleable by deformity due to underlying bone growth.

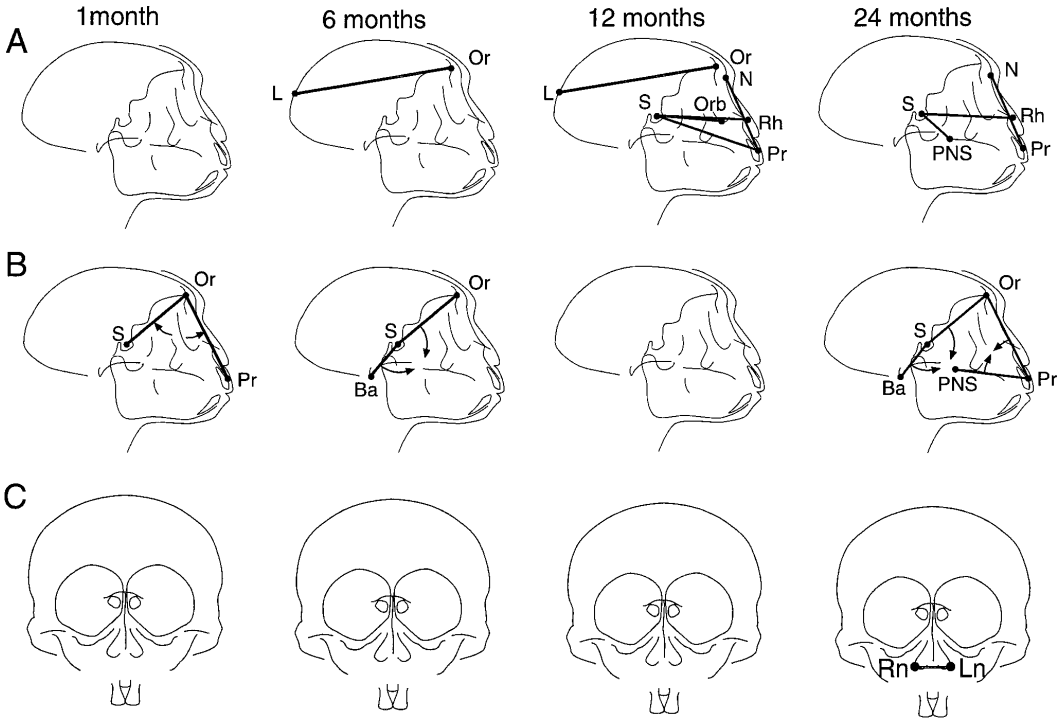

Fig. 4. Overview of craniofacial dimensions which were significantly correlated with cognitive impairment at age 1, 6, 12, and 24 months among all 18 animals ($P < 0.05$). **A, C:** All linear measures increased significantly as cognitive impairment increased. **B:** Angular measures changed in the direction indicated by arrows as cognitive impairment increased. Same abbreviations as in Figure 2.

Cranial size and shape

Interestingly, the OFCs in ethanol-exposed animals were consistently and often significantly larger than in the unexposed animals. This appears to be in contrast to the known relationship between in utero ethanol exposure and decreased brain size (Smith et al., '86; Autti-Ramo et al., '92). Clinically, OFC is used as a proxy measure for brain size, a proxy measure that is valid only if brain shape remains relatively constant. In this study, the increased OFC appears to be influenced more by increased cranial length (L-Or) than by increased brain size. Larger doses of ethanol initiated later in gestation have resulted in microcephaly and scaphocephaly in earlier nonhuman primate studies (Inouye et al., '85; Sheller et al., '88). Inouye et al. ('85) reported a tendency for increased cranial length in two macaques exposed to 2.5 g/kg and 4.1 g/kg ethanol on a weekly basis from 30 days postconception to birth. These findings suggest that ethanol may not only have an influence on the size of the cranium, but on cranial shape as well.

Correlations between midline craniofacial form and cognitive dysfunction

The strong correlations observed between the alcohol-induced craniofacial alterations and cognitive impairment further support the idea that midline craniofacial anomalies may be sensitive indicators of brain dysfunction (DeMeyer, '75). The FAS facial phenotype varies on a continuum and if measured on a continuous scale could serve as a more sensitive indicator of teratogenic outcome than the current practice of recording the FAS facial phenotype as simply present or absent. Preliminary analyses (unpublished) found strong, statistically significant correlations between increasing magnitude of expression of FAS facial phenotype and decreasing intelligence quotient (full-scale, performance, and verbal IQ) among children with prenatal alcohol exposure. The facial phenotype was measured on a continuous scale called the D-score (Astley and Clarren, '96) that reflects the combined magnitude of expression of palpebral fissure length, smooth philtrum, and upper lip thinness.

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Number of Axons in the Corpus Callosum of the Mature Macaca Nemestrina: Increases Caused by Prenatal Exposure to Ethanol

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ABSTRACT

The effects of prenatal exposure to ethanol on the number of callosal axons were examined. Pregnant *Macaca nemestrina* were treated with ethanol (1.8 g/kg b.wt.) 1 day per week during the first 6 weeks (Et6) or full 24 weeks (Et24) of gestation. Control macaques were intubated with an isocaloric amount of sucrose water (Ct). The mid-sagittal area of the corpus callosum in 4- to 5-year-old offspring was examined in magnetic resonance (MR) images and in fixed brains. The number of callosal axons was determined by using electron microscopy. In both MR images and fixed brains of macaques treated with ethanol, the corpus callosum was 26% larger than in the controls. The rostral portion was particularly affected by ethanol; it was 55% larger in Et6- and Et24-treated macaques. Axonal size and myelin thickness were unaffected by ethanol, but ethanol-treated macaques had more callosal axons (13.7×10^7) than did controls (9.4×10^7 axons). The increase in the rostral corpus callosum suggests that parietal and frontal cortices are particularly susceptible to ethanol. The altered callosal connectivity may be a component of the structural abnormalities that underlie executive processing problems associated with fetal alcohol syndrome. J. Comp. Neurol. 412:123–131, 1999.

Indexing terms: alcohol; axonal pruning; callosal axons; fetal alcohol syndrome; microencephaly; prefrontal cortex

One common manifestation of fetal alcohol syndrome (FAS) and models of FAS is microencephaly (e.g., Jones et al., 1973; Randall et al., 1977; Clarren et al., 1978; Miller, 1988a, 1996a). This reduced size is reflected in the numbers of neurons in the neocortex (Miller and Potempa, 1990; Mooney, 1997). For example, the total numbers of neurons in the primary somatosensory cortices of ethanol-treated rats are 33% fewer than those in control rats. A similar reduction is evident in each cortical layer and in the numbers of glia in each layer. A decreased size of brain is not inevitable in alcohol teratogenesis.

Despite generalized reductions in cell number, the brains of ethanol-treated rats are not miniaturized brains. For example, ethanol exposure affects the mix of neurons in each cortical layer. Ethanol-treated brains commonly have ectopic neurons, i.e., neurons with a specific phenotype that are located at inappropriate sites (e.g., Clarren et al., 1978; Miller, 1986a, 1988a, 1993, 1997; Miller et al., 1990). The connectivity of cortical neurons is also affected by ethanol exposure. The scope of dendritic trees (Shapiro et al., 1984; Pentney et al., 1984; Fabregues et al., 1985; Miller et al., 1990), the morphology of dendritic spines

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TABLE 1. Subjects[1]

		Ethanol treatment	
Subjects	Controls (n = 6)	6 weeks (n = 5)	24 weeks (n = 4)
34/LP*	x		
35/OH*	x		
36/SB*	x		
37/RS*	x		
38/TU	x		
40/DX*	x		
48/KX		x	
49/RG*		x	
50/SA*		x	
51/SC*		x	
52/SR*		x	
55/SH*			x
56/SI			x
58/EY*			x
60/KH*			x

[1]Three principal groups of macaques were examined: those treated with ethanol once per week for 6 weeks or for 24 weeks and controls (treated with sucrose and water once per week). Subjects scanned for magnetic resonance images are noted by asterisks.

(Stoltenburg-Didinger and Spohr, 1983; Miller et al., 1990), the density of cortical efferents (Miller and Al-Rabiai, 1994), and cortical synaptology (Al-Rabiai and Miller, 1989) are altered.

One of the major cortical pathways is the system of interhemispheric connections, i.e., the callosal system. The callosal system is responsible for giving the subject a unified, seamless image of the sensory world. Various reports show that a small number of children with severe FAS exhibit agenesis or dysgenesis of the corpus callosum (e.g., Clarren et al., 1978; Peifer et al., 1979; Pratt and Doshi, 1984; Schaefer et al., 1991; Riley et al., 1995; Swayze et al., 1997; Roebuck et al., 1998). It has been estimated that 6.8% of children with FAS have callosal defects as compared with 0.3% of the general population and 2.3% of those afflicted with developmental disabilities. In one sample, however, as many as 6 of 10 children with FAS exhibited partial or full callosal agenesis (Swayze et al., 1997).

Many data from animal studies support the clinical findings of callosal defects. For example, immature, ethanol-treated rodents have smaller corpora callosa than do controls (Wainwright and Gagnon, 1985; Wainwright and Fritz, 1985; Zimmerberg and Scalzi, 1989). Interestingly, these reductions are absent in mature animals suggesting that the corpus callosum is vulnerable to an ethanol-induced developmental delay. Recent evidence suggest that this delay is followed by an overshoot and that mature rats prenatally exposed to ethanol have more callosal projection neurons than do controls (Miller, 1997). To examine the apparent discrepancy between the human and experimental animal findings, we examined the corpora callosa of non-human primates that were treated with ethanol prenatally.

MATERIALS AND METHODS

Subjects

The subjects were pigtail macaques (*Macaca nemestrina*). These were a subset of the animals used in previous studies (Clarren and Astley, 1992; Clarren et al., 1992; Astley et al., 1995). The macaques that had been exposed for 3 weeks were not included in the present study because only one survived to 4–5 years of age. Brain tissue was obtained from 15 animals and magnetic resonance images were taken from 12 of these macaques (Table 1).

Care and feeding

The primates were clustered into three groups; two groups were exposed to ethanol prenatally and the third group was a control group. Care and handling of the animals was in accordance with institutional guidelines. Details about the care and feeding of the macaques have been described (Clarren and Astley, 1992; Clarren et al., 1992).

The dams of the ethanol-treated groups received a single dose of ethanol (1.8 g/kg b.wt.; Et) once a week for 6 weeks (Et6; i.e., the first quarter of gestation) or for 24 weeks (Et24; i.e., throughout the pregnancy). The Et6-fed animals were fed a sucrose solution (that was isocaloric/isovolumetric to the ethanol dose) once per week for the last 18 weeks of the pregnancy (i.e., from prenatal weeks 7 to 24). The dams of the control-treated macaques were given the sucrose solution (Ct) one day in each week of gestation.

All pregnant macaques were fed chow and water ad libitum. Nonhuman primates were consistently provided their aliquots of the Et or Ct on the same day of the week; for example, on gestational day (G) 3, G10, G17. . . , or on G5, G12, G19. . . In the cadre of nine Et-treated macaques used in the present study, the dosing was initiated on G3, G5, G6, or G7. On the eve of a dosing day (at 5:00 PM), all chow and water was removed. In the morning, the pregnant macaques were weighed and at 8:00 AM the animals were dosed. All pregnant animals were administered with the Et or Ct over a 5-minute period by means of soft nasogastric tubes. Chow and water was reintroduced at 5:00 PM.

Blood ethanol concentrations (BEC) were determined from each mother (Clarren et al., 1992). Samples of blood (1.0 ml) were taken 40–400 minutes post-dosing and BEC was measured with gas chromatography. Based on previous studies (Clarren and Astley, 1992; Clarren et al., 1992), peak BEC was attained 100 minutes after the Et was administered. At this time, the Et6- and Et24-treated macaques had mean BECs of 231 ± 18 mg/dl and 234 ± 14 mg/dl, respectively.

Magnetic resonance imaging

Animals lived in a complex community structure and were routinely subjected to psychometric tests (the outcome of some of these tests have been published elsewhere; Clarren et al., 1992). When the macaques were 3–5 years old, 12 of them (see Table 1) were sedated with an intramuscular injection of ketamine and xylazine (10 mg/kg b.wt.).

The procedures for obtaining the magnetic resonance (MR) images were the same as those described by Astley and colleagues (1995). Briefly, the macaques were placed in a prone position and aligned with the Frankfort horizontal plane perpendicular to the horizontal axis of a General Electric Signa whole body MR Scanner. The heads were placed inside a knee coil to accommodate the small size of a macaque head. A standard cranial series was obtained including T1-weighted images in the mid-sagittal plane (repetition time of 400–500 msec and echo time of 12 msec) were taken. A 16-cm field of view was used with a slice thickness of 3–4 mm. The images were analyzed with a Bioquant Image Analysis System, R & M Biometrics, Nashville, TN) to determine the cross-sectional area of the corpus callosum.

Tissue preparation

At the completion of the original study (Clarren et al., 1992), the 15 surviving macaques (the 12 used in the MR imaging study plus an additional one per treatment group; see Table 1) were euthanized for neuroanatomic evaluation. The macaques were 3.56–5.32 years old. Then, brain samples were prepared for electron microscopy by standard protocols. Briefly, animals were anesthetized with ketamine and xylazine and then killed by a three-stage intracardial perfusion. Each macaque was perfused with 200–300 ml of 0.10 M phosphate buffer (pH 7.4) in saline (PBS), 2–3 liter of 4.0% paraformaldehyde in 0.10 M phosphate buffer, and finally with 1 liter of 10% sucrose in PBS. The brain was removed from the cranium and stored in buffered 30% sucrose.

The brainstem and cerebellum were removed and the forebrain was hemisected. The wet weight of each whole brain was measured. The medial surface of the brain was imaged with the Bioquant System and the cross-sectional area of the corpus callosum was determined.

Electron microscopy

Samples from three sites in the corpus callosum (from the right hemisphere) were removed: the genu, body, and splenium. These areas interconnect the prefrontal cortex, primary and secondary somatosensory cortices, and primary and secondary visual cortices, respectively (LaMantia and Rakic, 1990a). Each block measured 1 mm high by 2 mm wide by 1 mm deep. The blocks were dehydrated, osmicated, and embedded in plastic. A series of ultrathin sections was taken from each block. Every eighth to tenth section was used in the analysis. These sections were cut in a sagittal plane to generate cross-sections of the corpus callosum.

A micrograph was taken of 5 non-overlapping fields (15μm × 15μm) in each of five representative sections per animal. Thus, a total of 25 micrographs was made for each callosal site for each animal. Three measures describing the composition of the corpus callosum in each field were taken by using the Bioquant System. (1) The size of each axon in the field was measured. This constituted the area within the outer aspect of the axolemma. (2) The thickness of the myelin was determined. Three independent measures from each myelin profile were examined and the mean was taken as the value for that axon. Each measurement was made at a site where the laminations were regular and parallel. (3) The number of axons included in each field was counted. Only axonal profiles that were fully within the defined area or intersected two of four sides of the measuring box (10μm x 10μm) were included in the tallies.

Analysis

In all phases of the study, the investigators were blind to the source of the sample. The mean values for the five non-overlapping fields per section were calculated. In turn, the mean (± the standard error of the mean) for the five sections from each callosal segment (i.e., the genu, body, and splenium) was determined. The latter mean was considered representative of the callosal segment that was used in the statistical analyses. Analyses of variance were used to assess differences among locations within the corpus callosum by prenatal treatment group. In cases where significant differences were detected, post-hoc Student-Newman-Keuls tests were performed.

TABLE 2. Effect of the Duration of Ethanol Exposure on Body and Brain Weight[1]

Parameter	Ct (n = 6)	Et6 (n = 5)	Et24 (n = 4)
Age (yr)	4.80 ± 0.18	4.95 ± 0.09	4.31 ± 0.32
Body weight (kg)	5.3 ± 0.8	6.9 ± 0.5	5.2 ± 0.6
Brain weight (g)	85.2 ± 8.7	88.3 ± 4.0	87.6 ± 4.8

[1]The age, body weight, and brain weight at sacrifice are given for macaques in the five treatment groups. The offspring of macaques were fed a sucrose control (Ct), fed ethanol once per week for 6 weeks (Et6), or fed ethanol once a week for 24 weeks (Et24). Each value is a mean (± the standard error of the mean).

RESULTS

Body and brain size

Data on the age, body weight, and brain weight of the macaques at sacrifice are provided in Table 2. Mean body weight was significantly ($P < 0.05$) greater in the Et6-treated animals than in the Ct- and Et24-treated macaques. The brain weight was unaffected by the prenatal exposure to ethanol.

Size of the corpus callosum

Magnetic resonance images of the living brain. The corpus callosum was measured in mid-sagittal MR images of 12 macaques (Fig. 1; Table 1). The mid-sagittal area of the corpus callosum was significantly ($F_{2,11} = 6.78$; $P < 0.019$) larger in the animals prenatally exposed to ethanol (Table 3). Student-Newman-Keuls tests show that the corpora callosa of both Et6- and Et24-treated macaques were significantly ($P < 0.05$) larger than those of the Ct-treated macaques. Differences between the two Et-treated groups were not statistically significant.

Planimetry of the corpus callosum in fixed brains. The corpus callosum was measured on the medial surface of each hemisphere of the 15 fixed brains (Fig. 2). No significant differences between the sizes of the sectioned corpora callosa in each hemisphere (i.e., in comparisons between the right and left sides from the same brain) were detected in any treatment group (Table 3). Although this was expected, the small differences (less than 2.0%) indicate that experimental error was inconsequential. The data from the two hemispheres were pooled and grand means (designated as "total" in Table 3) were generated based on animal units. An analysis of variance of these pooled data showed that the corpus callosum was larger in the Et6- (23.6%) and Et24-treated (22.3%) primates than in the controls ($F_{2,14} = 5.25$; $P < 0.023$).

The ethanol-induced increase was not even throughout the rostrocaudal extent of the corpus callosum. The corpus callosum was divided into two portions; the border between the two portions was at the level of the rostral thalamus where the body of the corpus callosum and the body of the fornix diverged. The size of the caudal segment was similar in Ct-, Et6-, and Et24-treated macaques. On the other hand, the rostral segment was significantly ($P < 0.05$) larger in the Et6- (62.6%) and Et-treated (50.3%) macaques than in the controls.

The corpus callosum in the fixed brains was smaller than it was in the MR images. It is interesting to note, that the difference was consistent among all of the treatment groups; about 8% (i.e., fixation ratios of about 0.92; see Table 3). The implications from these data were (1) that the fixation process caused a small amount of shrinkage independent of ethanol treatment and (2) that prenatal treatment did not affect the fixation ratio.

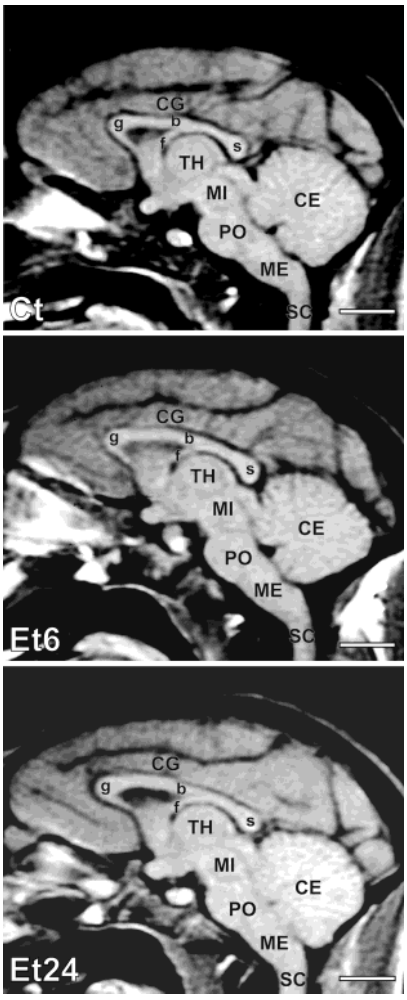

Fig. 1. MR images of ethanol- and control-treated macaques. These MR scans of the mid-sagittal planes of the brains of Ct- (top), Et6- (middle), and Et24-treated (bottom) macaques were taken within 0.5 years of the time of death. CE, cerebellum; CG, cingulate gyrus; b, body of the corpus callosum; f, fornix; g, genu of the corpus callosum; ME, medulla; MI, midbrain; PO, pons; s, splenium of the corpus callosum; SC, spinal cord; TH, thalamus. Scale bars = 1.0 cm.

TABLE 3. Size of the Corpus Callosum in Magnetic Resonance Images and Fixed Brains[1]

	Ct (n = 6)	Et6 (n = 5)	Et24 (n = 4)
MR images			
Right hemisphere ($\times 10^6$ µm^2)	86.2 ± 5.5	112 ± 4*	109 ± 10*
Rostral segment ($\times 10^6$ µm^2)	37.4 ± 3.3	60.8 ± 6.3*	56.2 ± 5.2*
Caudal segment ($\times 10^6$ µm^2)	48.8 ± 3.9	51.2 ± 4.5	53.0 ± 5.5
Fixed brains			
Right hemisphere ($\times 10^6$ µm^2)	81.1 ± 2.3	102 ± 6*	100 ± 8*
Rostral segment ($\times 10^6$ µm^2)	35.2 ± 1.8	54.9 ± 3.6*	52.9 ± 3.2*
Caudal segment ($\times 10^6$ µm^2)	45.8 ± 1.1	47.4 ± 2.5	47.0 ± 2.2
Left hemisphere ($\times 10^6$ µm^2)	82.3 ± 3.8	100 ± 4*	100 ± 8*
Total ($\times 10^6$ µm^2)	81.7 ± 3.5	101 ± 5*	100 ± 8*
Fixation ratio	0.941 ± 0.061	0.911 ± 0.054	0.917 ± 0.059

[1]The rostral and caudal segments were demarcated by the junction/separation of the body of the corpus callosum and the body of the fornix. The total size of the corpus callosum was compiled from the pooled data for the size of the corpus callosum in each hemisphere. The fixation ratio for the corpus callosum in the right hemisphere was calculated as the size of the corpus callosum in the fixed brains to the callosal size in the magnetic resonance images. Ct, sucrose control; Etb, fed ethanol once per week for 6 weeks; Et24, fed ethanol once per week for 24 weeks.
*Asterisks denote statistically significant ($P < 0.05$) differences relative to the size in the Ct-treated macaques.

Composition of the corpus callosum

The cross-sectional area of callosal axons, the thickness of the myelin, and the axonal density were measured in electron micrographs of the corpus callosum (Fig. 3). Each feature was examined at three locations, the genu, body, and splenium of the corpus callosum. Regardless of the treatment group and callosal location, only 10–15% of the callosal axons were non-myelinated.

In the control macaques, axonal size varied among the three locations. Axons in the genu were at best half the size of those at the other two locations (Fig. 4). This difference was statistically significant ($F_{2,4} = 36.2$; $P < 0.001$). A similar pattern was evident in the Et6- and Et24-treated macaques.

The mean thickness of the myelin sheaths paralleled the mean size of the axons (Fig. 5). Thus, the axons in the genu had the thinnest myelin and those in the splenium the thickest ($F_{2,4} = 16.1$; $P < 0.001$). At a particular callosal site, no differences among the Ct-, Et6-, and Et24-treated macaques were detected.

The mean axonal density was calculated as the quotient of the mean number of axons counted in a 100 µm^2 square. An analysis of variance ($F_{2,4} = 64.4$; $P < 0.001$) showed that density was affected by both the treatment group and the location in the corpus callosum. Regardless of the treatment group, the density was greatest in the genu and lowest in the splenium (Fig. 6). The only site where the axonal density was affected by an ethanol treatment was in the body. Here the density was significantly ($P < 0.05$) higher in the Et6- and Et24-treated macaques than in the controls.

An estimate of the total number of axons was calculated as the product of the size of the corpus callosum and the mean axonal density (Fig. 7). The latter value was determined as the mean of the axonal density at the three sites. Accordingly, the Et6- and Et24-treated macaques had significantly more (48.8% and 41.2%, respectively) axons than did the controls ($F_{2,12} = 14.4$; $P < 0.001$). No differences between the two ethanol treatment groups were observed; that is, the duration of the ethanol exposure had no effect.

DISCUSSION

Size and axonal content of the corpus callosum in normal non-human primates

The corpus callosum is the largest commissure in the primate brain. Its cross-sectional area in the *M. nemestrina* is 81.7 mm^2. This is similar to the size of the corpus callosum in the *M. mulatta* (76.4 mm^{2}d Rakic, 1990a). In both the *M. nemestrina* and the rhesus monkey, axonal density varies with location; the density in the genu is about twice that in the body and the splenium. On the other hand, regardless of location, the present study shows that the density of axons in the corpus callosum of the *M.*

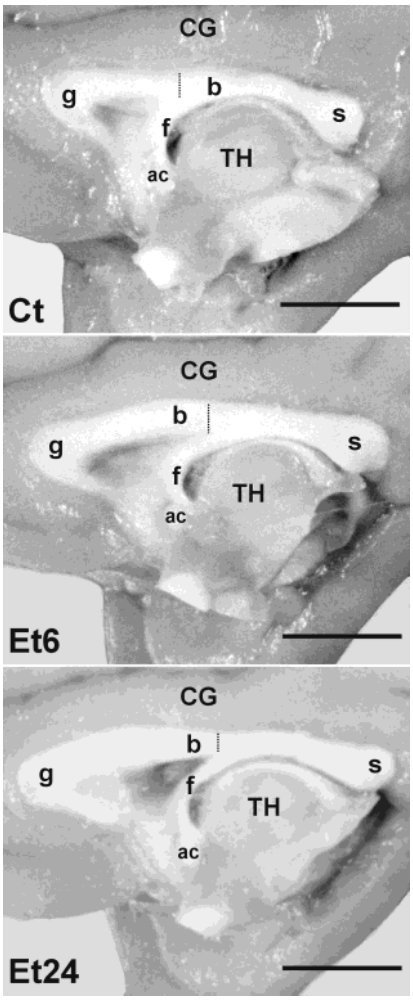

Fig. 2. Corpora callosa of macaques prenatally exposed to ethanol. The medial aspects of the same brains as those depicted in Figure 1 are shown; Ct- (top), Et6- (middle), and Et24-treated (bottom) macaques. The dotted line through the body of the corpus callosum identifies the border between the rostral and caudal segments. ac, anterior commissure; b, body of the corpus callosum; CG, cingulate gyrus; g, genu of the corpus callosum; f, fornix; s, splenium of the corpus callosum; TH, thalamus. Scale bars = 1.0 cm.

nemestrina (1.18 axons/μm^2 is 40–50% greater than in the rhesus monkey (0.766 axons/μm^2; LaMantia and Rakic, 1990a). The net result is that the estimated number of callosal axons in the *M. nemestrina* (94.2×10^6 axons) is 68.2% higher than in the *M. mulatta* (56.0×10^6 axons; LaMantia and Rakic, 1990a). It must be kept in mind that the weights of the mature brains of the two macaque species are similar (*cf.* the present results and Holloway and Heilbroner, 1992). The inter-species differences be-

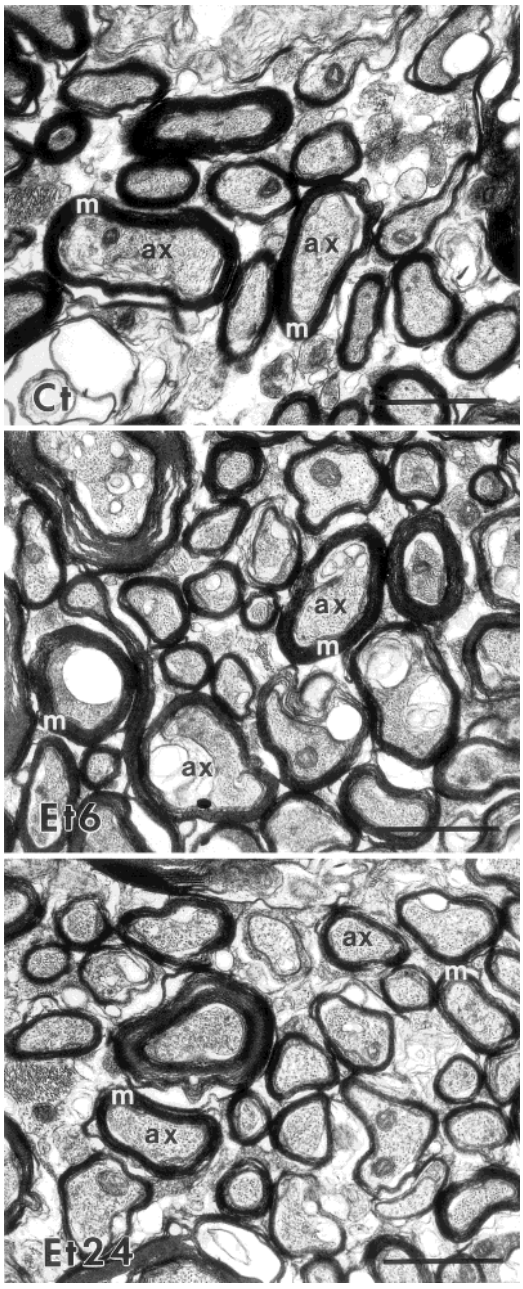

Fig. 3. Ultrastructure of the genu of the corpus callosum. Myelinated axons (ax) are the most common feature of the corpus callosum in Ct- (top), Et6- (middle), and Et24-treated (bottom) macaques. m, myelin. Scale bars = 2.0 μm.

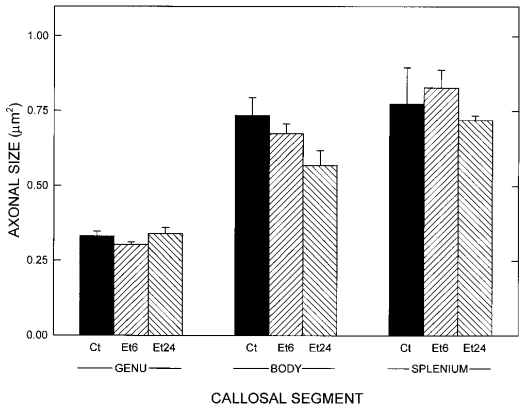

Fig. 4. Axonal size. The mean cross-sectional area of axons in a 100 μm² box (± the standard error of the mean) was plotted for the five treatment groups. A separate mean was calculated for axons in the genu (left), body (middle), and splenium (right) of the corpus callosum. At each callosal site, no differences among treatment groups were detected.

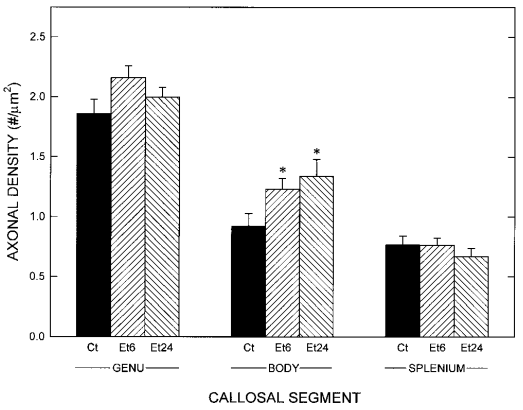

Fig. 6. Axonal density. The packing density of axons varied with the location; the density was greatest rostrally and lowest caudally. Prenatal treatment only had a significant effect ($P < 0.05$; noted by asterisks) on axonal density in the body of the corpus callosum. There, the density of callosal axons was greater in all animals treated with the Et, regardless of the presentation (e.g., Et6 or Et24).

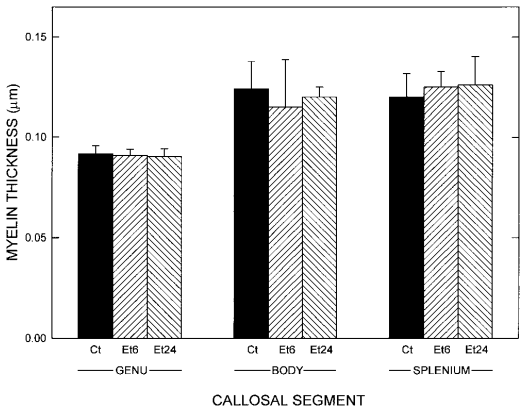

Fig. 5. Myelin thickness. At each callosal site, the mean thickness of the myelin sheath was not significantly different in the Ct-, Et6-, and Et24-treated macaques. T-bars denote the standard errors of the means.

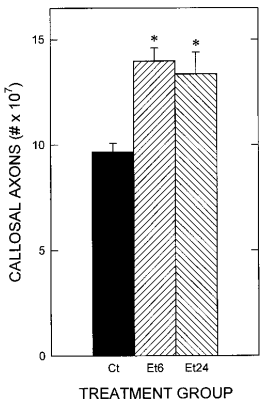

Fig. 7. Total number of axons in the corpus callosum. Regardless of whether the Et was provided over 6 weeks (Et6) or 24 weeks (Et24), the estimated total number of callosal axons was greater in the Et-treated macaques than it was for controls. Statistically significant differences ($P < 0.05$) are noted by asterisks.

tween the *M. nemestrina* and the *M. mulatta* in callosal size are small. After all, despite no change in brain weight, the size of the corpus callosum in the *M. mulatta* is 42.7% larger than cross-sectional area of the corpus callosum in another macaque, the *M. fascicularis* (Holloway and Heilbroner, 1992).

Species differences in ethanol-induced changes in callosal size

Exposure to moderate amounts of ethanol, once per week during gestation for as little as 6 weeks, increases the size of the corpus callosum in the macaque. This ethanol-induced increase in callosal size results from an increase in the number of callosal axons. Furthermore, the increase occurs regardless of how long the fetus is exposed to ethanol (i.e., 6 or 24 weeks).

In addition to the present study, data from rat investigations also show that prenatal exposure to ethanol increases the number of callosal projection neurons (Miller, 1997). Such findings are at variance with the data from various studies of children with severe brain alterations in FAS (e.g., Clarren et al., 1978; Peifer et al., 1979; Pratt and Doshi, 1984; Schaefer et al., 1991; Riley et al., 1995; Swayze et al., 1997). These clinical studies show that such children with severe brain abnormalities have a higher incidence of callosal agenesis or dysgenesis than that for

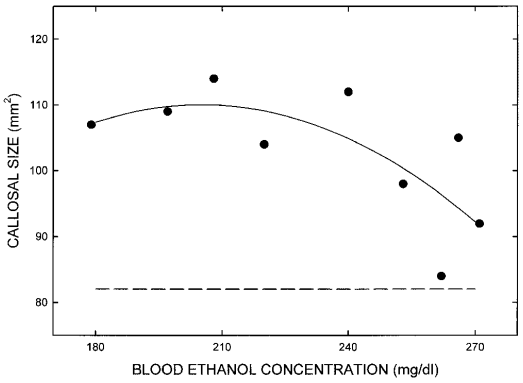

Fig. 8. Effects of blood ethanol concentration on callosal size. The data on the callosal size were plotted against peak blood ethanol concentration for each animal. The solid line depicts the second order curve that best fits the data ($P < 0.05$) and the dashed line describes the mean callosal size in the controls.

the general population. Such clinical data, however, must be interpreted with caution. There is the great risk that by focusing on children with FAS who have the more severe or obvious brain disruptions, the data sample may not be generalizable to all children with fetal alcohol damage. The clinical studied are biased in that they present data from severely affected children. The monkeys in the present study evidently are less severely affected because they are not microencephalic. The results of a recent MR imaging study support this contention (Streissguth and Bookstein, personal communication). In this study, children with a wide range in severity of CNS dysfunction in FAS and alcohol-related neurodevelopmental disorder were examined. The range of callosal defects varies widely; in fact, some of the children exhibit enlarged corpora callosa.

One key factor determining the effect of ethanol on callosal size may be the peak BEC. Ethanol-treated macaques and rodents with larger corpora callosa (Miller, 1997; present study) had BECs of <250 mg/dl. In contrast, the mothers of rodents and people exhibiting callosal damage likely had BECs of >250 mg/dl. Interestingly, a curious relationship emerges when the data for the callosal size are plotted against BEC (Fig. 8). Exposure to moderate BEC results in a modest increase in callosal size. The maximal effect is evident with BEC between 205 and 240 mg/dl. At BEC of >250 mg/dl, callosal size falls with BEC. These data should be interpreted with caution, however, because all animals in the present study were treated with the same amount of ethanol and peak BEC can vary within an individual animal by 25% or more (Bonthius and West, 1990). Nevertheless, the data are compelling and it is important to note that dose-dependent effects for dopamine neurochemistry in macaques (Astley et al., 1995) and for hippocampal morphology in rats (Miller, 1995) have also been described.

Critical windows of ethanol exposure

The timing of ethanol exposure may have profound teratogenic effects. Sulik has shown that mice treated with ethanol on G7 exhibit the full array of craniofacial malformations that are characteristic of FAS (Sulik, 1984). The brains of these animals also are malformed, particularly midline structures such as the septal nuclei and the corpus callosum (e.g., Sulik and Johnston, 1982; Schambra et al., 1989). The BEC of these mice was extremely high, 500–600 mg/dl. Rats exposed to ethanol through much of the prenatal period (including G8 and G9; the days when gastrulation occurs in the rat) also have callosal damage (Zimmerberg and Scalzi, 1989; Miller, 1997).

It is difficult to draw parallels between the timing of rat and macaque development. If we use the time of gastrulation and the timing of cortical neuronogenesis as bases of comparisons, however, some meaningful conclusions can be drawn. Gastrulation occurs on G8 or G9 in the rat and on G19 or G20 in the macaque. Cortical neurons in macaques are generated between G45 and G102 (Rakic, 1974, 1978) and between G12 and G21 in the rat (Bruckner et al., 1976; Miller, 1988a,b). Thus, based on studies with mice (Sulik, 1984), it can be predicted that macaques exposed to ethanol on G19 or G20, would experience craniofacial and midline brain damage. Data show that the macaques exposed to ethanol on G19 or G20 do, in fact, exhibit craniofacial anomalies (Astley et al., 1999).

The data for the macaque and the rodent are not wholly consistent. The lack of a difference between the Et6- and Et24-treated macaques suggests that brain alterations can result from episodic ethanol exposure before embryonic implantation, but before the period of cortical neuronogenesis. In contrast, cortical damage in the rat may not be caused by such early exposure. For example, the proliferation of cortical progenitors in the rat is unaffected by exposure to ethanol between G6 and G9, whereas exposure between G12 and G15 or between G18 and G21 significantly alters cell proliferation (Miller, 1996b).

Regional specific effects of ethanol

The rostral portion of the macaque corpus callosum is the most affected by prenatal exposure to ethanol. This segment interconnects the frontoparietal lobes in the two hemispheres. In the rat we know that both motor (frontal) and somatosensory (parietal) cortices are profoundly affected by ethanol (e.g., Miller, 1987, 1997; Miller and Potempa, 1990). Although no comparable data are available for the non-human primate, there is reason to suspect that somatosensory cortex in the macaque brain is also targeted by prenatal ethanol treatment.

Evidence implicating the frontal lobe is interesting in light of data from children with FAS. The size of frontal cortex is disproportionately altered in children with FAS (S.N. Mattson, personal communication). By itself, this reduction may be meaningless, but such children also exhibit abnormalities in executive functions (Kodituwakku et al., 1995; Kopera-Frye et al., 1996) and executive functions have been attributed to prefrontal processing (e.g., Eslinger et al., 1992; Bechara et al., 1996, 1998). Thus, the abnormal structure of frontal cortex and likewise the altered numbers of axons in the rostral segment of the corpus callosum may underlie prefrontal dysfunction of executive activities.

Ethanol-induced overgrowth of axons and dendrites

Studies in the rodent show that early exposure to ethanol can promote the growth of axons. Prenatal exposure to ethanol induces an increase (1) in the number of callosal projection neurons in the somatosensory cortex of

the rat (Miller, 1997), (2) in the number of corticospinal projection neurons in somatosensory and motor cortices (Miller, 1987), and (3) in the number of their descending axons in the lower pyramidal tract (Miller and Al-Rabiai, 1994). Recent evidence shows that ethanol treatment promotes axonal growth by cultured hippocampal neurons (Clamp and Lindsley, 1998).

Ethanol-induced overgrowth is not restricted to axonal systems. Prenatal exposure to ethanol also can induce the postnatal hypergrowth of dendrites. Corticospinal projection neurons in somatosensory cortex of Et-treated rats and cerebellar Purkinje neurons have more complex dendritic trees (i.e., more branches) and longer dendrites than do neurons in controls (Pentney et al., 1984; Miller et al., 1990). These data were based on rats that were treated with ethanol from G6 to G21. Similar data were garnered from mice exposed to ethanol only on G10 and G11 (R.F. Mervis, personal communication), that is, early in the period of cortical neuronogenesis (Angevine and Sidman, 1961; Bruckner et al., 1976; Gardette et al., 1982; Miller, 1988a,b).

Callosal (e.g., O'Leary et al., 1981; Ivy and Killackey, 1982; LaMantia and Rakic, 1990b) and corticospinal axons (e.g., Stanfield et al., 1982; O'Leary and Stanfield, 1986) and the dendrites of cortical pyramidal neurons (Miller, 1981, 1986b, 1988b) undergo considerable pruning during early development. We hypothesize that ethanol reduces the pruning process. Various data support this hypothesis. In the developing macaque, the number of callosal axons reaches a maximum of 3.5-fold more than that in the adult (LaMantia and Rakic, 1990b). Et-treated macaques have only 0.45-fold more callosal axons than do controls. This is consistent with the notion that the pruning of callosal axons that normally occurs in all developing macaques is partially blocked by prenatal exposure to ethanol. Further support comes from a study of pyramidal tract axons in developing rats. The number of these axons falls during early postnatal development, but the fall is not as precipitous or profound in Et-treated rats as it is in controls (Miller and Al-Rabiai, unpublished results). The increases in axonal and dendritic fields could be affected (1) by blocking the action of a pruning regulator (e.g., Sato et al., 1994; Frisen et al., 1998) or (2) by facilitating the action of an agent(s) that promotes neuritic growth such as a neurotrophin. Interestingly, ethanol potentiates neurotrophin activity in vitro so that the ethanol-treated cultured neurons elaborate more neurites (Messing et al., 1993; Zou et al., 1993, 1995).

In summary, macaques exposed to moderately high levels of ethanol exhibit increases in the sizes of their corpora callosa and in the numbers of callosal axons. These alterations likely result from interference with substances that regulate normal neuronal growth, e.g., neurotrophins. It is generally assumed that cognitive deficits result from reductions in axonal and/or dendritic fields, however, evidence that ethanol-induced cognitive deficits are caused by an overabundance of axons and dendrites is building.

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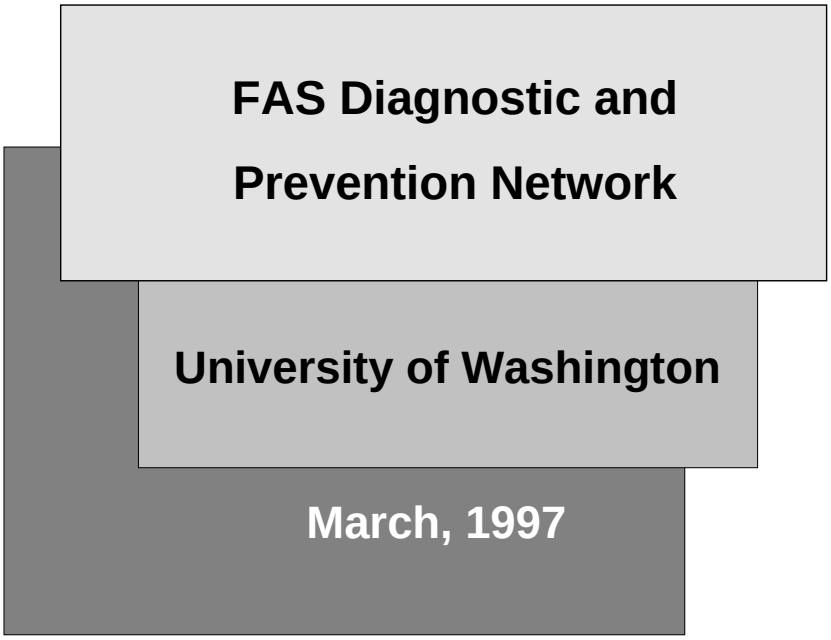
Diagnostic Guide for Fetal Alcohol Syndrome and Related Conditions

The 4-Digit Diagnostic Code



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Contents

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Preface

This Diagnostic Guide is a work-in-progress. Based on our own experience and feedback from others, we continue to make modifications that enhance accuracy, improve clarity, and increase ease of usage. Until now, the volume has been formatted in a ring binder to ease revisions, but the large demand for copies had led to our decision to reproduce the work in this format at this time. It remains our plan to update this Guide on an annual basis. We hope you will find this new approach to fetal alcohol exposure diagnosis helpful and broadly applicable.

I. Introduction

Fetal alcohol syndrome (FAS).

FAS is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. The definition of the fetal alcohol syndrome has changed little since the 1970's when the condition was first described and refined. The condition has been broadly characterized by pre- and/or postnatal growth deficiency, a characteristic set of minor facial anomalies, and evidence of prenatal alteration in brain function such as microcephaly from birth, neurologic problems without postnatal antecedents, or complex patterns of functional disability.

The difficulty with diagnosing FAS and other disabilities associated with in utero alcohol exposure.

For the trained clinician, dysmorphologist, or clinical geneticist there is little difficulty in making the diagnosis of FAS when the anomalies in growth, face, and brain are all extreme and the alcohol exposure is conclusive and substantial. But the features are not dichotomous, that is either normal or clearly abnormal. Rather, the features, and indeed the history of alcohol exposure, all range along separate continua from normal to clearly abnormal and distinctive.

In the absence of accurate, reproducible and unbiased methods for measuring and recording the severity of exposure and outcome in individual patients, diagnoses will continue to vary widely from clinic to clinic. From a clinical perspective, diagnostic misclassification leads to inappropriate patient care, increased risk for secondary disabilities and missed opportunities to achieve prevention. From a public health perspective, diagnostic misclassification leads to inaccurate estimates of incidence and prevalence. Inaccurate estimates thwart efforts to allocate sufficient social and health care services to this high risk population and preclude accurate assessment of primary prevention intervention efforts. From a clinical research perspective, diagnostic misclassification reduces the power to identify between-group contrasts within studies. Non-standardized diagnostic methods limit the ability to compare outcomes between studies.

A new approach to diagnosis.

This manual introduces a new approach to diagnosis; the "*4-Digit Diagnostic Code*". The four digits reflect the magnitude of expression of four key diagnostic features of FAS in the following order: (1) growth deficiency, (2) the FAS facial phenotype, (3) brain dysfunction, and (4) gestational alcohol exposure. The magnitude of expression of each feature is ranked independently on a 4-point Likert scale with 1 reflecting complete absence of the FAS feature and 4 reflecting a strong "classic" presence of the FAS feature.

Benefits of the new diagnostic approach.

This new approach:

1. Greatly increases diagnostic precision and accuracy.
2. Better characterizes the disabilities of alcohol exposed individuals who do not have FAS.
3. Documents the presence of alcohol exposure without judging its causal role.
4. Utilizes a clinical nomenclature that separates a patient's functional disabilities from their exposure history.

While this document might at first appear overly complex and perhaps daunting, one will find that this new diagnostic approach is logical and easy to use and will greatly facilitate the proper description and classification of patients presenting with all possible combinations of outcomes and exposure.

Other syndromes

The methods of diagnosing fetal alcohol syndrome and related conditions arise from the larger fields of teratology and dysmorphology (clinical genetics). It is essential to remember that isolated features in many birth defect syndromes overlap with FAS. A few examples of conditions often easily confused with FAS include Aarskog syndrome, fragile-x syndrome, fetal hydantoin syndrome and Noonan syndrome. Furthermore it is likely that this diagnostic approach to organizing dysmorphic features and issues of cognitive and behavioral problems could be used for patients exposed to other potentially teratogenic substances instead of or in addition to alcohol. This diagnostic guide is "FAS specific" but this in no way should imply that the diagnostician need not consider alternate syndromic diagnoses and medical conditions at all times.

II. FAS Diagnostic Evaluation Form

The FAS Diagnostic Evaluation Form guides the clinical team in the collection, recording, and interpretation of all key information required to make an accurate and precise alcohol related diagnosis. The form also serves as a template for efficient generation of the final medical summary note. This form is a "work-in-progress". It continues to be revised based on the collective experience of the Washington State FAS Diagnostic and Prevention Network, to improve accuracy, clarity and ease of use.

Where is the information for the Diagnostic Form obtained from?

The information recorded in the Diagnostic Form is obtained from four primary sources:

1. The New Patient Information Form completed by the caregivers (Appendix).
2. Previous medical / psychological / educational assessments.
3. Assessments administered by the clinical staff at the time of the diagnostic evaluation.
4. The caregiver/patient interview conducted at the time of the diagnostic evaluation

When is the form completed and by whom?

The form is completed by the clinical staff before and during the patient's clinic visit.

FAS Diagnostic Evaluation Form

Medical # 11_____ Clinic 12 _____ Date seen in Clinic 13 ___ / ___ / ___

Patient's Name: 14_____ 15 _____ 16 _____ Age(y) 17_____ Birth Date 18 ___ / ___ / ___
First Middle Last

Name person(s) accompanying patient 19_____

Relationship(s) to patient 110_____ 111Patient's Gender M F

Patient's Race/Ethnicity:112 _____

Form completed by:113 _____

Diagnosis made by: 114 _____

Diagnosis(es): 115 _____

_____

_____

4-Digit Diagnostic Code Grid

(See instructions in Diagnostic Guide for FAS and Related Conditions)

116 ____ ____ ____ ____

Growth Deficiency	FAS Facial Features	Brain Dysfunction		Growth	Face	Brain	Alcohol		Gestational Alcohol
significant	severe	definite	4					4	high risk
moderate	moderate	probable	3					3	some risk
mild	mild	possible	2					2	unknown
none	absent	unlikely	1					1	no risk

GROWTH

At Birth

Birth weight: 117_____ (gms/lb.oz.) centile for gestational age 118_____

Birth length 119_____ (cm/inches) centile for gestational age 120_____

Gestational age at birth 121_____ (weeks)

Highest Weight and Height Centiles Recorded Prior to 13.0 Years of Age

wgt 122_____ (kg/lbs.), 123_____ (centile), age (yr) 124_____

hgt 125_____ (cm/inches), 126_____ (centile), age (yr) 127_____, parent adjustment 128_____cm

Lowest Weight and Height Centiles Recorded

wgt 129_____ (kg/lbs.), 130_____ (centile), age (yr) 131_____

hgt 132_____ (cm/inches), 133_____ (centile), age (yr) 134_____, parent adjustment 135_____cm

Current Weight and Height

wgt 136_____ (kg/lbs.), 137_____ (centile), age (yr) _____

hgt 138_____ (cm/inches), 139_____ (centile), age (yr) _____, parent adjustment 140_____cm

Birth Parent's Heights

mother's hgt 141_____/_____ (in/cm), fathers's hgt 142_____/_____ (in/cm), mid-parent hgt 143_____cm

ABC Summary Score for Growth Deficiency

144*Circle the ABC Scores for:*

See instructions in Diagnostic Guide for FAS

	Height	Weight
≤ 3rd centile = **C**	C	C
>3rd and ≤ 10th centile = **B**	B	B
> 10th centile = **A**	A	A

This ABC Score reflects the patient's growth between 145_____ years and 146_____ years of age.

FACIAL FEATURES (and other physical findings)

CURRENT PHENOTYPE: (Age _____ years)

Direct measures

Right palpebral fissure length (Hall) Right 21_____ (cm) 22_____ (SD)

Left palpebral fissure length (Hall) Left 23_____ (cm) 24_____ (SD)

Inner canthal distance (right to left inner canthi) (Hall) 25_____ (cm) 26_____ (SD)

	Not Present		*Mildly Present*		*Definitely Present**	
	1	2	3	4	5	
Flat philtrum 27	_____	_____	_____	_____	_____	(*flat*)
Thin upper lip 28	_____	_____	_____	_____	_____	(*thin*)

Clinic Photograph **Internal Measure** true size 29 _____ units 210(_____)

Was a facial photograph taken? 211Yes ___, No ___ photo size 212 _____ units 213(_____)

Right palpebral fissure length / innercanthal distance: 214_____ / 215_____ = 216_____

	Not Present		*Mildly Present*		*Definitely Present**		Upper Lip
	1	2	3	4	5		
Flat philtrum 217	_____	_____	_____	_____	_____	(*flat*)	Circularity*
Thin upper lip 218	_____	_____	_____	_____	_____	(*thin*)	219 _____

Compute photo facial Dscore 220_____ from formula below*

*(Astley&Clarren,1996, Figure 1) Dscore = 0.74 - 5.73 (R. palpebral/innercanthal ratio) + 1.17 (philtrum Likert score) + 0.16 (upper lip Likert score)

PAST PHENOTYPE: 221(Age _____ years)

Source of information 222(photograph _____, text record _____)

Left palpebral fissure length:223_____ (arbitrary units / cm) 224_____ (SD)

Right palpebral fissure length / innercanthal distance: 225_____ / 226_____ = 227_____

	Not Present		*Mildly Present*		*Definitely Present**		Upper Lip
	1	2	3	4	5		
Flat philtrum 228	_____	_____	_____	_____	_____	(*flat*)	Circularity*
Thin upper lip 229	_____	_____	_____	_____	_____	(*thin*)	230 _____

Compute photo facial Dscore 231_____ from formula above*.

ABC SUMMARY SCORE of Facial Phenotype

(See instructions in the Diagnostic Guide for FAS for deriving the ABC Score and translating it into a 4-Digit Diagnostic Code)

5-Point Likert Scale for Philtrum & Lip	Standard Deviation Scale for Fissures	232 *Circle the ABC Scores for:* Palpebral Fissures	Smooth Philtrum	Thin Upper Lip
4 or 5	≤ -2 SD	C	C	C
3	>-2 SD and ≤ -1 SD	B	B	B
1 or 2	> -1 SD	A	A	A

All Additional Physical Findings (*circle or write in*) 233 epicanthal folds, ptosis, clown eyebrows, hockey stick palmar creases,

_____

_____

_____ Page 2

ORGANIC BRAIN DYSFUNCTION

Examiner's Clinical Judgment of Severity of Outcome
Circle: 0 = Unable to Judge, 1 = Normal, 2 = Mildly Abnormal, 3 = Severely Abnormal

Severity **STRUCTURAL**

0 1 2 3 31OFC 32_____ (cm) 33_____ (centile, SD) at 34_____ years of age.

0 1 2 3 35Structural anomalies on CT/MRI 36 _____

0 1 2 3 37Other: 38 _____

NEUROLOGIC

0 1 2 3 39Seizure Disorder: type 310 _____ age at onset 311 _____(yrs)

0 1 2 3 312Gross motor 313_____

0 1 2 3 314Fine motor 315 _____

0 1 2 3 316Quick Neurological Screening Test score 317 _____

0 1 2 3 318Other neurologic signs 319 _____

FUNCTIONAL ("Objective" Indicators) Provide most recent test scores

0 1 2 3 320**Intellectual**: (test/version) 321 _____ age 322_____ yr/mos

FSIQ or equiv.323 _____ VIQ324 _____PIQ325 _____ PercOrg326 _____ VerbComp327 _____ FreeDis328 ___

Inf329 ___ Sim330 ___ Ari3331___ Voc332 ___ Com333 ___ Dig334 ___ PicC335 ___ PicA336 ___ Blo337 ___ Obj338___ Cod339 ___ Maz340 ___

Sent341 _____ AH342 _____ GeomD343 ___ DigS344 _____ SymSrch345 ___ / Verb Comp346 _____ NV ReasonVis347 _____ Memory348 _____

SeqPr348a ___ Simul Pr349 ___ Ach350 ___ NV351 ____Age(s) of previous intelligence tests 352ab_____ yrs

0 1 2 3 353**Achievement** (test/version) 354_____ age 355_____ yr/mos

Subtest	Score	Type of Score (stand., %, age equiv., T, Z, etc)
356a _____	356b_____	356c _____
357a _____	357b_____	357c _____
358a _____	358b_____	358c _____
359a _____	359b_____	359c _____
360a _____	360b_____	360c _____
361a _____	361b_____	361c _____
362a _____	362b_____	362c _____
363a _____	363b_____	363c _____
364a _____	364b_____	364c _____
365a _____	365b_____	365c _____

Age(s) of previous Achievement tests 366ab_____ yrs

0 1 2 3 367**Adaptation** (test/version) 368_____ age 369_____ yr/mos

Composite Score Name	Score	Type of Score (stand., %, age equiv., T, Z, etc)
370a _____	370b_____	370c _____
Subtest		
371a _____	371b_____	371c _____
372a _____	372b_____	372c _____
373a _____	373b_____	373c _____
374a _____	374b_____	374c _____

Age(s) of previous Adaptation tests 375ab_____ yrs

(See the "Diagnostic Guide for FAS" for instructions on deriving the 4-Digit Diagnostic Code for CNS Dysfunction) Page 3

ORGANIC BRAIN DYSFUNCTION (Continued)

Examiner's Clinical Judgment of Severity of Outcome
Circle: 0 = Unable to Judge, 1 = Normal, 2 = Mildly Abnormal, 3 = Severely Abnormal

Severity

0 1 2 3 **Behavior/Social Competence**[41](test name/version) [42]_____age [43]_____ yr/mos

Subtest	Score	Type of Score (standard, %, age equiv., T, Z, etc.)
[44a]	[44b]	[44c]
[45a]	[45b]	[45c]
[46a]	[46b]	[46c]
[47a]	[47b]	[47c]
[48a]	[48b]	[48c]
[49a]	[49b]	[49c]
[410a]	[410b]	[410c]

Age(s) of previous Behavioral/Social tests[411ab]_____ yrs

0 1 2 3 **Neuropsychological**[412] (circle battery of individual tests administered) age range [413a]_____to [413b]_____ yrs

Haltead-Reitan[414a] VMI[b] WSCT[c] CPT[d] WRAML[e] COWAT[f] Rey[g] Paired Asstes[h]
Luria-Nebraska[i] Bender-G[j] STROOP[k] CVLT-C[l] Clock Test[m] Ravens[n] SSM[o] Cons Tri[p]
Other (specify)[q]_____

Aberrant areas [415]_____

_____

_____

0 1 2 3 **Language**[416]

Expressive (test name)	Score	Type of Score	
[417a]	[417b]	[417c]	age [417d]_____ yr/mos
[418a]	[418b]	[418c]	age [418d]_____ yr/mos
Receptive (test name)	**Score**	**Type of Score**	
[419a]	[419b]	[419c]	age [419d]_____ yr/mos
[420a]	[420b]	[420c]	age [420d]_____ yr/mos
Other (test name)	**Score**	**Type of Score**	
[421a]	[421b]	[421c]	age [421d]_____ yr/mos
[422a]	[422b]	[422c]	age [422d]_____ yr/mos

0 1 2 3 Mental State Reasoning Test[423] (Univ. Washington, Coggins) age [424]_____ yr/mos
1st Order [425] (Belief [a] P / F Justification [b] P / F) 2nd Order [426](Belief [a] P / F Justification [b] P / F)

0 1 2 3 Narrative Test[427] (Univ. Washington, Coggins) age [428]_____ yr/mos
Bus Story [429] _____ Frog Story[430] _____

0 1 2 3 **Developmental**[431] (test/version) [432]_____age [433]_____ yr/mos

Subtest	Score	Type of Score (standard, %, age equiv., T, Z, etc)
[434a]	[434b]	[434c]
[435a]	[435b]	[435c]
[436a]	[436b]	[436c]
[437a]	[437b]	[437c]
[438a]	[438b]	[438c]
[439a]	[439b]	[439c]
[440a]	[440b]	[440c]

(See the "Diagnostic Guide for FAS" for instructions on deriving the 4-Digit Diagnostic Code for CNS Dysfunction) Page 4

ORGANIC BRAIN DYSFUNCTION (Continued)

Examiner's Clinical Judgment of Likelihood of Organic Brain Dysfunction
Circle: 0 = Unable to Judge, 1 = Unlikely, 2 = Somewhat Likely, 3 = Very Likely

FUNCTIONAL ("Subjective" Indicators) These observations are intended to support, not define, clinical impressions

Organicity Problem Areas Presence of problem: Circle: [Y = Yes, N = No, U = Unknown, T = Too young to assess]

0 1 2 3 **Planning**[51]

[Y N U T] [52]Needs considerable help organizing daily tasks
[Y N U T] [53]Cannot organize time, [54][Y N U T] doesn't understand concept of time
[Y N U T] [55]Difficulty in carrying out multi-step tasks
[Y N U T] [56]Other [57]_____

0 1 2 3 **Behavioral Regulation/ Sensory Motor Integration**[58]

[Y N U T] [59]Poor management of anger / tantrums
[Y N U T] [510]Mood swings
[Y N U T] [511]Impulsive, [512][Y N U T] compulsive, [513][Y N U T] perseverative,
[Y N U T] [514]Inattentive
[Y N U T] [515]Inappropriate activity level [516][Y N U T] high, [517][Y N U T] low
[Y N U T] [518]Lying/stealing
[Y N U T] [519]Over- or [520][Y N U T] under-reactivity to stimuli (e.g., noise, pain)
[Y N U T] [521]Other[522] _____

0 1 2 3 **Abstract Thinking / Judgment**[523]

[Y N U T] [524]Poor judgment, [525][Y N U T] Cannot be left alone
[Y N U T] [526]Concrete, unable to think abstractly
[Y N U T] [527]Other[528] _____

0 1 2 3 **Memory / Learning / Information Processing**[529]

[Y N U T] [530]Poor memory, inconsistent retrieval of learned information
[Y N U T] [531]Slow to learn new skills
[Y N U T] [532]Does not seem to learn from past experiences
[Y N U T] [533]Problems recognizing consequences of actions
[Y N U T] [534]Problems with information processing speed and accuracy
[Y N U T] [535]Other[536] _____

0 1 2 3 **Spatial Memory**[537]

[Y N U T] [538]Gets lost easily, has difficulty navigating from point A to point B
[Y N U T] [539]Other [540] _____

0 1 2 3 **Social Skills and Adaptive Behavior**[541]

[Y N U T] [542]Behaves at a level notably younger than chronological age
[Y N U T] [543]Poor social/adaptive skills
[Y N U T] [544]Other[545] _____

0 1 2 3 **Motor/Oral Motor Control**[546]

[Y N U T] [547]Poor/delayed motor skills, [548][Y N U T] poor balance
[Y N U T] [549]Other[550] _____

Psychiatric Diagnoses[551]_____

[Y N U T][552] ADHD, [Y N U T][553] ADD

Medication(s)	Response (+, -, none)	Medication(s)	Response (+, -, none)
[554a] _____	[554b] _____	[555a] _____	[555b] _____
[556a] _____	[556b] _____	[557a] _____	[557b] _____
[558a] _____	[558b] _____	[559a] _____	[559b] _____

(See the "Diagnostic Guide for FAS" for instructions on deriving the 4-Digit Diagnostic Code for CNS Dysfunction) Page 5

MATERNAL ALCOHOL USE

Alcohol consumption of the birth mother

Before pregnancy: average number of drinks per drinking occasion: [61] _____

maximum number of drinks per occasion: [62] _____

number of drinking occasions per week: 63 _____

Type of alcohol consumed most often:64 ___wine, ___beer, ___liquor, ___unk, ___other 65 _____

During pregnancy: average number of drinks per drinking occasion: 66 _____

maximum number of drinks per occasion: 67 _____

number of drinking occasions per week: 68 _____

Type of alcohol consumed most often:69 ___wine, ___beer, ___liquor, ___unk, ___other 610 _____

Trimester(s) in which alcohol was consumed611 ___ 1st ___2nd ___3rd ___ unk. ___ not applicable

---

	No	Suspected	Yes	Unknown
Was the birth mother ever diagnosed with alcoholism? 612	___	_____	___	_____
Was the birth mother ever reported to have a problem with alcohol? 613	___	_____	___	_____
Did the birth mother ever receive treatment for alcohol addiction? 614	___	_____	___	_____

Who reported the mother's alcohol use during pregnancy? 615 ____ birth mother, ____ a direct observer, ____ an individual or source that did not directly observe drinking during pregnancy

Reported use of alcohol during pregnancy is:616 ___reliable, __questionably reliable, __of unk. reliability

Other information:617 _____

_____

Summary Measure of Alcohol Exposure

Circle the 4-Digit Diagnostic Code Rank in the table below that best reflects the patient's gestational Alcohol Exposure Category.

4-Digit Diagnostic Code Rank	Gestational Alcohol Exposure Category	Description
4	High Risk	• Report by the birth mother or directly from other individual who saw the mother drink during pregnancy *and* • Report of exposure likely to produce BAC's over 100mg% weekly, early in pregnancy.
3	Some Risk	• Report by birth mother, other direct observer, or reliable source *and* • Drinking occurred in gestation in frequencies and volumes less than in category (4) or otherwise unspecified.
2	Unknown Risk	• Gestational exposure is simply not known or information is of uncertain reliability
1	No Risk	• The mother reliably acknowledges no exposure to alcohol in pregnancy, or minimal exposure

CO-MORBIDITIES

PRENATAL 71

High risk	Some risk	Unknown risk	No risk
4	3	2	1

Prenatal

1. Poor prenatal care:[72] ____ no ____ suspected ____ yes ____ unknown
2. Complications/trauma (specify)[73]_____

Genetics

1. Parental learning difficulties (i.e., Special Ed., ADD, MR, did not complete high school, etc.)
   [74]Mother ____ no ____ suspected ____ yes ____ unknown
   [75]Father ____ no ____ suspected ____ yes ____ unknown
   If yes, specify (maternal)[76]_____
   (paternal)[77]_____
2. [78]Other conditions of heritability or malformation that may be significant in this case. (*specify*)
   _____

Other Teratogenic Exposures[79]

_____

_____

POSTNATAL [710]

High risk	Some risk	Unknown risk	No risk
4	3	2	1

Perinatal Difficulties[711]

_____

_____

Issues of Nurture

1. Abuse: Physical[712] _____ Sexual[713] _____
2. Disrupted Placement History[714] ____ no ____ suspected ____ yes ____ unknown
3. Other[715] _____
   _____
   _____

Other Issues (e.g., head injuries, fever, chronic substance abuse)[716]

_____

_____

_____

FAS Diagnostic and Prevention Network
Preliminary Summary and Recommendations

The final medical summary will be sent to you in approximately two weeks.

Name: _____ Clinic: _____

Birth Date: _____ / _____ / _____ Clinic Date: _____ / _____ / _____Clinic phone: _____

Diagnostic Outcome: _____

Result(s) of assessment(s) performed in Clinic (if applicable):

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Recommendations for Follow-Up

A. Medical Issues

_____

_____

_____

_____

_____

_____

_____

FAS Diagnostic and Prevention Network
Preliminary Summary and Recommendations (*Continued*)

The final medical summary will be sent to you in approximately two weeks.

Name: _____ Birth Date: _____ / _____ / _____

Recommendations for Follow-Up

B. Developmental, Educational, Vocational, Mental Health, and Family Issues

III. Diagnostic Evaluation Form Instructions

A. The 4-Digit Diagnostic Code

What are the 4 Digits?

The four digits reflect the magnitude of expression of four key diagnostic features of FAS in the following order: (1) growth deficiency, (2) the FAS facial phenotype, (3) brain dysfunction, and (4) gestational alcohol exposure. The 4-Digit Diagnostic Code is generated at the completion of the diagnostic evaluation using information recorded on the FAS Diagnostic Evaluation Form. The code is created by filling in the grid below which appears on page one of the Diagnostic Form.

4-Digit Diagnostic Code Grid

				3	4	4		4		
significant	severe	definite	(4)		X	X		X	(4)	high risk
moderate	moderate	probable	(3)	X					(3)	some risk
mild	mild	possible	(2)						(2)	unknown
none	absent	unlikely	(1)						(1)	no risk
Growth Deficiency	**FAS Facial Features**	**Brain Dysfunction**		Growth	Face	Brain		Alcohol		**Gestational Alcohol**

Figure 1. 4-Digit Diagnostic Code grid. This grid is filled in to illustrate how the Diagnostic Code 3444 is derived. This code is one of eight which qualifies as a diagnosis of FAS.

How are the 4 Digits ranked?

The magnitude of expression of each feature is ranked independently on a 4-point Likert scale with 1 reflecting complete absence of the FAS feature and 4 reflecting a strong "classic" presence of the FAS feature. Specific guidelines for ranking the magnitude of each of the FAS features are presented in Section III.B.

How many 4-Digit Diagnostic Codes are there?

There are 256 possible 4-Digit Diagnostic Codes ranging from 1111 to 4444. The 256 codes and their corresponding clinical names are listed in numerical order in Section VI.

We have created diagnostic categories for all potential codes, even though to date we do not expect to see all of these situations in clinic. For example, 1111 reflects a normal exam in an individual who was definitely not exposed to alcohol. Such patients are seen by primary physicians daily, but are unlikely to be referred to an FAS clinic. Other codes like 4441 would represent a “classic” clinical presentation of FAS with a confirmed absence of alcohol exposure during gestation. We have never seen such a case (or phenocopy), but we may some day.

How many different Clinical Diagnostic Categories are there?

Each 4-Digit Diagnostic Code falls into one of 22 unique Clinical Diagnostic Categories (labeled A through V). A list of the 22 Diagnostic Categories is presented in Section IV. A list of the 4-Digit Diagnostic Codes, which fall within each Clinical Diagnostic Category, is presented in Section V.

What are the names of the Clinical Diagnostic Categories?

A series of terms are used in varying combinations to name the 22 diagnostic categories. They include:

- **Sentinel Physical Findings:**
  The adjective *"sentinel"* refers to key physical findings that, in combination, are highly sensitive and specific to in utero alcohol exposure. These include a unique cluster of minor facial anomalies (short palpebral fissures, thin upper lip and a smooth philtrum) and growth deficiency. These sentinel features serve as necessary and sufficient criteria for establishment of the physical component of an FAS diagnosis. Other physical findings may be detected instead of or in addition to the sentinel findings which may suggest alternate or additional conditions. The findings may also present as isolated features which may or may not be caused by in utero alcohol. There are places on the Diagnostic Evaluation Form to record and interpret other physical findings.

- **Static Encephalopathy:**
  The term *"encephalopathy"* refers to any physical abnormality in the brain. Such abnormalities can vary in magnitude from structural defects that are apparent on an image like a CT scan to micro-cellular abnormalities that can only be confirmed with tissue samples or neurochemical analysis. The term *"static"* means that the physical abnormality in the brain is unchanging, neither progressing or regressing. The term *"static encephalopathy"* is used in this diagnostic system when the patient presents with cognitive/behavioral dysfunction which is accompanied by structural, neurologic, and/or psychometric measures which strongly support the presence of structural brain abnormalities. The term does not define or suggest any specific pattern of structural abnormality or cognitive/behavioral dysfunction.

- **Neurobehavioral Disorder:**
  This term is used in this diagnostic system when the patient presents with cognitive/behavioral dysfunction, but structural, neurologic and psychometric measures do not unequivocally support the presence of structural brain abnormalities. Reasonably specific conditions like attention deficit disorder and dyslexia, for example could be referred to as neurobehavioral disorders.

- **Alcohol (Exposed, Not Exposed, Exposure Unknown):**
  This term is used to reflect the exposure status of the fetus. It is <u>not</u> to be used to link alcohol exposure to outcome.

- **Fetal Alcohol Syndrome:**
  The term FAS is used to refer to patients who present with the full compliment of sentinel physical findings, static encephalopathy and were alcohol exposed.
- **Atypical Fetal Alcohol Syndrome:**

This term is introduced for use with a relatively small group of patients who have static encephalopathy, most of the sentinel physical findings of FAS, and were alcohol exposed. Given the fact that variable presentation is the rule rather than the exception after teratogenic exposure in gestation, we felt it was appropriate to establish this marginal category.

The names assigned to each diagnostic category reflect the patient's clinical outcome and alcohol exposure. The names are listed in Sections IV and V. The first three categories (A through C) meet the criteria for a clinical diagnosis of FAS and are named as such. The fourth category (D) applies to the patient who presents with all of the features of FAS, but has a confirmed *absence* of gestational alcohol exposure. This category is referred to as an FAS Phenocopy and has yet to be observed.

The remaining 19 categories (E through V) do not meet the minimum criteria for FAS and are subsequently named to reflect the Likert ranking of each digit in the 4-Digit Diagnostic Code. For example, a code of 4342 is the Diagnostic Category called "*sentinel physical findings / static encephalopathy (alcohol exposure unknown)*". Many of these patients might have previously been referred to variably as having possible fetal alcohol effects (PFAE), alcohol related birth defects (ARBD), or alcohol related neurodevelopmental disorder (ARND). This new nomenclature supersedes all of these terms.

The following nomenclature pattern is used:

- Growth deficiency and facial characteristics are physical features. When either feature receives a rank of 3 or 4, the patient is referred to as having a *sentinel physical finding*.

- When brain dysfunction receives a rank of 2, the condition is referred as a *neurobehavioral disorder*. When brain dysfunction receives a rank of 3 or 4, the condition is referred to as *static encephalopathy*

- When alcohol exposure receives a rank of 1, there is a *confirmed absence of gestational alcohol exposure*. When alcohol exposure receives a rank of 2, *alcohol exposure is unknown.* When alcohol exposure receives a rank of 3 or 4, *gestational alcohol exposure is confirmed.*

Which new Diagnostic Categories represent the category we use to call FAE?

Diagnostic Categories E through I would have previously been referred to as "fetal alcohol effects", "alcohol related birth defects" or "alcohol related neurobehavioral disorder". Categories J through V are new categories which describe a large number of patient groups who have never been adequately classified or described in the past.

How do you explain the diagnosis to the patient?

At the end of this manual (Section VII) are summary explanations for each of the 22 Clinical Diagnostic Categories. These summaries can be used as the first page of the patient's final medical summary note.

III. Diagnostic Evaluation Form Instructions

B.1. Scoring Growth Deficiency

What type of growth deficiency are we looking for?

We are looking for growth deficiency characteristic of a teratogenic insult, not characteristic of postnatal environmental factors such as nutritional deprivation or chronic illness. We want to answer the question *'What is the patient's growth potential after controlling for parental height and postnatal environmental influences?'* Growth deficiency of teratogenic origin is likely to present as a relatively consistent impairment over time (i.e., the patient's growth follows the normal curve, but is below genetic expectation for family background). In contrast, growth deficiency due to postnatal environmental influences is likely to present as periodic fluctuations in the curve. *Separating the two growth patterns requires astute clinical judgment.*

The method described below allows one to rank a patient's overall growth pattern on a single 4-point Likert scale with 1 equaling normal and 4 equaling significantly deficient. Not all patients will have complete growth curves available, therefore, a guide is provided below for prioritizing the ranking of the patient's growth over time

Method for ranking the growth component of the 4-Digit Diagnostic Code

A. Height should be age and gender adjusted and should be adjusted for parental height, if possible.

B. Weight should be age and gender adjusted. Weight is not adjusted for height. Normal growth charts are provided in Section VIII.

C. For ranking purposes, the growth curve is separated into two parts:
   1. Prenatal growth (birth measures)
   2. Postnatal growth (all measures collected after birth)

   Select the part with the greatest deficiency in height.

   If the prenatal height centile is lower than all postnatal height centiles, proceed to section D for instructions on how to rank prenatal growth.

   If any of the postnatal height centiles are lower than the prenatal height centile, select the point or consecutive points on the curve that reflect the lowest height centiles which cannot be attributed to postnatal environmental influences such as nutritional deprivation or chronic illness. If the height deficiency is reflected in a series of points on the curve, as opposed to a single point, rank the level of deficiency based on the centile range where the majority of the points fall. Proceed to section D for instructions.

D. Rank the level of deficiency of the height and weight centiles for the section of the curve with greatest height deficiency by circling A, B or C in the ABC Summary Score table at the bottom of page 1 of the FAS Diagnostic Evaluation Form. This ABC Summary Score table is duplicated below as Table 1.

Table 1: Deriving the ABC Summary Score

ABC Rank	Centile Range	Circle the ABC-Score for: Height	Weight
C	$\leq 3^{rd}$	C	C
B	$>3^{rd}$ and $\leq 10^{th}$	B	B
A	$>10^{th}$	A	A

E. Next, refer to Table 2 to determine the *4-Digit Diagnostic Code Rank* of the Height-Weight ABC Score Combination recorded in Table 1. Transfer the resulting 4-Digit Diagnostic Code Rank for growth to the 4-Digit Diagnostic Code Grid at the top of page 1 of the FAS Diagnostic Evaluation Form.

Table 2: Converting the ABC-Score to a 4-Digit Diagnostic Code Rank

4-Digit Diagnostic Code Rank	Growth Deficiency Category	Height-Weight ABC-Score Combinations
4	Severe	CC
3	Moderate	CB, BC
2	Mild	CA, BB, AC
1	None	BA, AB, AA

Example for Scoring Growth Deficiency

Patient's Growth Record:

	Age (years)	Height Centile	Weight Centile
birth	0.0	5 %	2 %
	1.5	10 %	15 %
	5.0	12 %	20 %
	7.0	12 %	10 %
	15.5	15 %	30 %

Let's say clinical records rule-out any environmental influence on postnatal measures.

Scoring:

- Priority would be placed on ranking the birth measures because the birth height centile is lower than all postnatal height centiles recorded.
- Birth height would be ranked **$>3^{rd}$ and $\leq 10^{th}$** (or Rank B) in Table 1.
  Birth weight would be ranked **$\leq 3^{rd}$** (or Rank C) in Table 1.

Table 1: Deriving the ABC Summary Score

		Circle the ABC-ScoreS for:	
ABC Rank	Centile Range	Height	Weight
C	$\leq 3^{rd}$	C	**C**
B	$>3^{rd}$ and $\leq 10^{th}$	**B**	B
A	$>10^{th}$	A	A

- The Height-Weight ABC-Score Combination would be **BC** according to Table 2.
- The Growth Deficiency Category would be **Moderate** according to Table 2.
- Moderate growth deficiency receives a rank of **3** in the 4-Digit Diagnostic Code in Table 2.

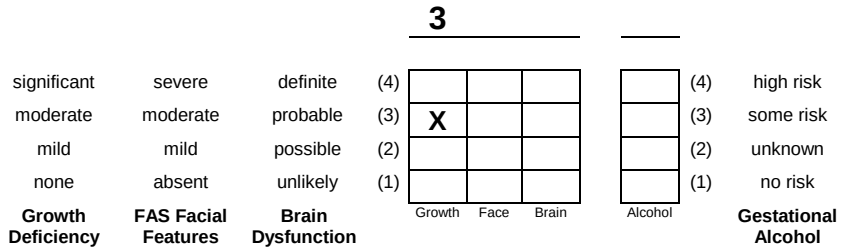
Table 2: Converting the ABC-Score to a 4-Digit Diagnostic Code Rank

4-Digit Diagnostic Code Rank	Growth Deficiency Category	Height-Weight ABC-Score Combinations
4	Severe	CC
3	**Moderate**	CB, **BC**
2	Mild	CA, BB, AC
1	None	BA, AB, AA

The number **3** would be transferred to the 4-Digit Diagnostic Code Grid on page 1 of the FAS Diagnostic Evaluation Form (as duplicated below).

Result:

4-Digit Diagnostic Code Grid



III. Diagnostic Evaluation Form Instructions

B.2. Scoring the Facial Phenotype

Method for ranking the facial phenotype component of the 4-Digit Diagnostic Code

A. Palpebral fissure lengths are measured in standard deviations from the norm. The palpebral fissures are adjusted for age and when possible, race. More precise measures are obtained from upward-looking eyes. Use the Hall (1989) palpebral fissure length chart provided in Section VIII.

B. The upper lip and philtrum are measured on 5-point photographic Likert scales using Figure 1 from the Astley & Clarren (1996) which is duplicated on the next page. Lips should be gently closed with no smile (Figure 2).

C. Rank the level of expression of the fissures, philtrum, and upper lip by circling A, B, or C in each column in the ABC Summary Score table at the bottom of page 2 of the FAS Diagnostic and Evaluation Form. This table is duplicated below as Table 3.

Table 3: Deriving the ABC Summary Score

5-Point Likert Scale for Philtrum & Lip	Standard Deviation Scale for Fissures	Circle the ABC-Scores for: Palpebral Fissures	Smooth Philtrum	Thin Upper Lip
4 or 5	≤ -2 SD	C	C	C
3	>-2 SD and ≤ -1 SD	B	B	B
1 or 2	> -1 SD	A	A	A

D. Next refer to Table 4 to determine the *4-Digit Diagnostic Code Rank* based on the ABC-Score Combination derived from Table 3. Transfer the resulting 4-Digit Diagnostic Code Rank for face to the 4-Digit Diagnostic Code Grid on page 1 of the FAS Diagnostic Evaluation Form.

Table 4: Converting the ABC-Score to a 4-Digit Diagnostic Code Rank

4-Digit Diagnostic Code Rank*	Level of Expression of FAS Facial Features	Palpebral Fissure - Philtrum - Lip ABC-Score Combinations
4	Severe	CCC
3	Moderate	CCB, CBC BCC
2	Mild	CCA, CAC, CBB, CBA, CAB, CAA BCB, BCA, BBC, BAC ACC, ACB, ACA, ABC, AAC
1	Absent	BBB, BBA, BAB, BAA ABB, ABA, AAB, AAA

* If facial measures are available at more than one age, score the age when the FAS phenotype is expressed the most. If FAS features are never expressed, score the face between the ages of 3 and 10 years, or at any age if this age range is not available.

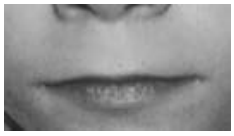
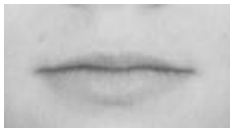
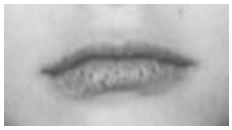
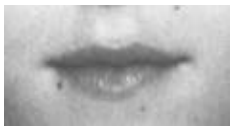
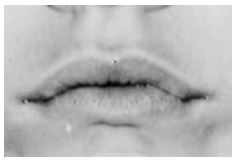
Philtrum/Upper Lip	Philtrum Likert Scale	Upper Lip Likert Scale	ABC Scale
	5	5	C
	4	4	C
	3	3	B
	2	2	A
	1	1	A

Figure 1. Pictorial examples of the 5-point Likert scales and the ABC scale used to rank upper lip thinness and philtrum smoothness. It is important that the individual's lips are gently closed with no smile.

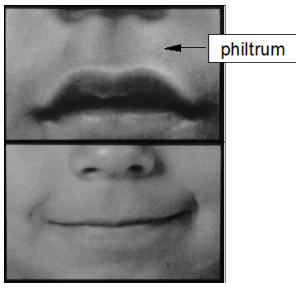


Figure 2. This is the same person with and without a smile. A smile can make the philtrum and upper lip appear smoother and thinner respectively than they truly are.

Example for Scoring Facial Phenotype

Patient measurements at 10 years of age:

- Palpebral fissure lengths = 2.5 cm which is < -2 SD's from the norm.
- Philtrum smoothness received a score of 5 on the 5-Point photographic Likert scale in Figure 1.
- Upper lip thinness received a score of 3 on the 5-Point photographic Likert scale in Figure 1.

Scoring

- The palpebral fissure lengths receive a Score of “C” in Table 3.

  A philtrum score of 5 corresponds to a score of “C” in Table 3.

  A lip score of 3 corresponds to a score of “B” in Table 3.

- The ABC-Score Combination for Fissure - Philtrum - Lip is **CCB**.

Table 3: Deriving the ABC Summary Score

5-Point Likert Scale for Philtrum & Lip	Standard Deviation Scale for Fissures	Circle the ABC-Scores for: Palpebral Fissures	Smooth Philtrum	Thin Upper Lip
4 or 5	≤ -2 SD	**C**	**C**	C
3	>-2 SD and ≤ -1 SD	B	B	**B**
1 or 2	> -1 SD	A	A	A

- A score of CCB indicates that the level of expression of the FAS Facial Features is **MODERATE**.

- A MODERATE expression of the FAS facial features receives a rank of **3** in the 4-Digit Diagnostic Code.

Table 4: Converting the ABC-Score to a 4-Digit Diagnostic Code Rank

4-Digit Diagnostic Code Rank	Level of Expression of FAS Facial Features	Palpebral Fissure - Philtrum - Lip ABC-Score Combinations
4	Severe	CCC
3	**Moderate**	**CCB**, CBC BCC
2	Mild	CCA, CAC, CBB, CBA, CAB, CAA, BCB, BCA, BBC, BAC ACC, ACB, ACA, ABC, AAC
1	Absent	BBB, BBA, BAB, BAA ABB, ABA, AAB, AAA

- Transfer the number **3** to the 4-Digit Diagnostic Code Grid on page 1 of the FAS Diagnostic Evaluation Form (duplicated below).

Result

4-Digit Diagnostic Code Grid

				3					
significant	severe	definite	(4)					(4)	high risk
moderate	moderate	probable	(3)		X			(3)	some risk
mild	mild	possible	(2)					(2)	unknown
none	absent	unlikely	(1)					(1)	no risk
Growth Deficiency	**FAS Facial Features**	**Brain Dysfunction**		Growth	Face	Brain	Alcohol		**Gestational Alcohol**

III. Diagnostic Evaluation Form Instructions

B.3. Scoring Brain Dysfunction

Method for ranking the brain dysfunction component of the 4-Digit Diagnostic Code

A. Rank Definitions

Brain dysfunction is the most significant disability for individuals with FAS and related conditions and accuracy in this area is important and yet often elusive. The 4-point Brain Dysfunction Scale (Table 5) allows the clinician to separate patients with clear evidence of organic brain damage (static encephalopathy, category 4) from patients without evidence of organic brain damage (category 1). It also introduces two intermediate categories for describing patients who, in the clinician's judgment, cannot be clearly placed in categories 1 or 4.

Category 4

It is our impression that "organic brain damage" or static encephalopathy is readily diagnosed by clinicians when structural anomalies of the brain are detected or when permanent neurologic findings of presumed prenatal origin are found. Many, but not all, clinicians will also accept evidence of mental retardation (i.e., I.Q. score ≤ 60) as an alternate diagnostic confirmation.

Any positive finding(s) recorded under the Structural or Neurologic headings of the Organic Brain Dysfunction section (page 3) of the FAS Diagnostic Evaluation Form are sufficient to classify a patient as Category 4.

Category 3

Through our experience with hundreds of patients who have been exposed to potentially teratogenic doses of ethanol, we have found that many would not qualify as having static encephalopathy using the definition above, but neither could the possibility that they have static encephalopathy be dismissed out of hand. These are typically patients with IQ scores that are above the range clearly indicative of mental retardation, but who often have wide variations in IQ subtest scores, and in addition, have problems with executive functioning, memory and learning, language pragmatics, social adaptation, attention, and/or hyperactivity. These patients have problems that seem likely due to underlying brain structure or function rather than to adverse postnatal environmental experiences, yet do not meet the criteria for Category 4. Patients should be scored in category 3 when they do not meet the criteria for category 4, yet have enough psychometric data to strongly suggest to the clinician that organicity is probable.

Deficiencies recorded under the Functional (“Objective” Indicators) heading of the Organic Brain Dysfunction section (pages 3 and 4) of the FAS Diagnostic Evaluation Form serve to support a Category 3 classification. To date, criteria for the number of deficiencies that must be present to warrant a Category 3 classification has not been established. Classification in this category is made through clinical judgment and the overall weight of evidence obtained. As data from patients in

this category are reviewed over time, we anticipate that the categorical determinants will be more specifically defined. In using this category, care must be taken that sufficient evidence is available to justify "probable" CNS dysfunction.

Category 2

This score should be given to two subgroups of patients. All patients in category 2 have histories of behavioral and/or cognitive problems that strongly suggest organic brain dysfunction should be a consideration. One group of patients has not yet had the types of testing that would move them into Categories 3 or 4 if positive. The reason for this lack of testing is usually because the patients are too young to be tested. The other group of patients are those who have had testing that did not reveal compelling evidence for category 3 or 4 classification, and yet, in the clinician's judgment, a strong possibility of organicity can not be wholly dismissed. Alternative testing and/or later date testing should usually be considered. If adequately sensitive and appropriate testing has been carried out without clear evidence of CNS dysfunction, it is unlikely a Category 2 classification would be given.

Deficiencies recorded under the Functional (“Subjective” Indicators) heading of the Organic Brain Dysfunction section (page 5) of the FAS Diagnostic Evaluation Form serve to support a Category 2 classification. To date, criteria for the number of deficiencies that must be present to warrant a Category 2 classification have not been established. The classification is made through clinical judgment and the overall weight of evidence obtained.

Category 1

Patients are placed in this category when no problems in the areas of behavior and learning are discerned.

B. Completing the Organic Brain Dysfunction section of the FAS Diagnostic Evaluation Form

The organic brain dysfunction section appears on pages 3 through 5 of the FAS Diagnostic Evaluation Form.

Structural, Neurologic and Objective Functional Indicators (Pages 3 and 4)

Structural, neurologic, and “objective” functional indicators of organic brain damage are recorded on pages 3 and 4 of the diagnostic form. These pages serve as a place to record pertinent structural, neurologic, and psychometric information available on the patient to date.

The clinician is asked to rank the level of abnormality of each outcome on the following Likert scale: 0 = unable to judge, 1 = normal, 2 = mildly abnormal and 3 = severely abnormal. This ranking process is based solely on the clinician’s clinical judgment and serves to guide him/her in classifying overall organic brain damage into Category 3 or 4 (static encephalopathy) if appropriate.

Subjective Functional Indicators (Page 5)

"Subjective" functional indicators of organic brain dysfunction are recorded on page 5 of the diagnostic form. The findings on this page are used as a guide to support a Category 2 (neurobehavioral disorder) classification. The literature on the behavioral characteristics of individuals with FAS and related conditions suggests that common problem areas are among those listed page 5. The literature also implies that these areas are problematic because of aberrations in brain processing rather than the result of oppositionality or other emotional disturbance (a concept to be further tested).

Within each "problem area" are a list of key indicators. The clinician is asked to record which indicators are present in the patient, after considering age, by circling **Y**es, **N**o, **U**nknown or **T**oo young to assess. The clinician is also asked to rank the overall likelihood that each "problem area" is explained in part or in whole by organic brain dysfunction using the following scale:

Very Likely	**(3)**	The caregiver and/or patient are able to provide complete information in the interview and the information they provide strongly supports the problem area is organic in origin because the patient can not perform in that area at an appropriate level for age and intelligence rather than will not perform.
Somewhat Likely	**(2)**	The distinction between the patient can not perform and the patient will not perform is less clear because the person being interviewed is unable to provide adequate information or because the origin of the problem is mixed.
Unlikely	**(1)**	Adequate information is available and there is no evidence of a brain processing deficit.
Unable to Judge	**(0)**	Information in this area is not available either because assessments have not been made yet or the child is too young to be assessed in the area.

Table 5: Deriving the 4-Digit Diagnostic Code Rank for Organic Brain Dysfunction

4-Digit Diagnostic Code Rank*	Organic Brain Dysfunction Scale	Confirmatory Findings
4	**Definite** *referred to as static encephalopathy*	● microcephaly, OFC ≤ -2 S. D. *and / or* ● abnormalities on brain images diagnostic of prenatal alteration *and / or* ● evidence of persistent neurologic findings likely to be of prenatal origin *and / or* ● I. Q. score ≤ 60
3	**Probable** *referred to as static encephalopathy*	● Substantial deficiencies or discrepancies across multiple areas of brain performance such as cognition, achievement, adaptation, neurologic "soft" signs, and language. Generally three or more areas should be found aberrant.
2	**Possible** *referred to as neurobehavioral disorder*	● Historical information / personal observations strongly suggest that the possibility of an "organic" condition exists, but data to this point does not permit a category 3 or 4 classification.
1	**Absent**	● No problems likely to have an organic component are presented.

* Transfer the resulting 4-Digit Diagnostic Code Rank for Organic Brain Dysfunction to the 4-Digit Diagnostic Code Grid on page 1 of the FAS Diagnostic Evaluation Form.

III. Diagnostic Evaluation Form Instructions

B.4. Scoring Alcohol Exposure

Table 6: Deriving the 4-Digit Diagnostic Code Rank for Alcohol Exposure

4-Digit Diagnostic Code Rank*	Gestational Alcohol Exposure Category	Description
4	High Risk	● Report by the birth mother or directly from another individual who saw the mother drink during pregnancy *and* ● Report of exposure likely to produce blood alcohol concentrations > 100mg% weekly, early in pregnancy.
3	Some Risk	● Report by birth mother, other direct observer, or reliable source *and* ● Drinking occurred in gestation in frequencies and volumes less than in category (4) or otherwise unspecified.
2	Unknown Risk	● Gestational exposure is simply not known or information is of uncertain reliability
1	No Risk	● The mother reliably acknowledges no exposure to alcohol in pregnancy, or minimal exposure (i.e. 1 drink less than once per month)

* Transfer the resulting 4-Digit Diagnostic Code Rank for Alcohol Exposure to the 4-Digit Diagnostic Code Grid on page 1 of the FAS Diagnostic Evaluation Form.

IV. Diagnostic Categories

The 256 Diagnostic Codes can be logically grouped into 22 Diagnostic Categories

Category	Name
A	Fetal alcohol syndrome (alcohol exposed)
B	Fetal alcohol syndrome (alcohol exposure unknown)
C	Atypical fetal alcohol syndrome (alcohol exposed)
D	Fetal alcohol syndrome phenocopy (no alcohol exposure)
E	Sentinel physical findings / static encephalopathy (alcohol exposed)
F	Static encephalopathy (alcohol exposed)
G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
H	Neurobehavioral disorder (alcohol exposed)
I	Sentinel physical findings (alcohol exposed)
J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)
K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
L	Static encephalopathy (alcohol exposure unknown)
M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
N	Neurobehavioral disorder (alcohol exposure unknown)
O	Sentinel physical findings (alcohol exposure unknown)
P	No cognitive/behavioral or sentinel physical findings detected (alcohol exposure unknown)
Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
R	Static encephalopathy (no alcohol exposure)
S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
T	Neurobehavioral disorder (no alcohol exposure)
U	Sentinel physical findings (no alcohol exposure)
V	No cognitive/behavioral or sentinel physical findings detected (no alcohol exposure)

V. 4-Digit Diagnostic Codes Within each Diagnostic Category

Category	Diagnostic Name and Codes
A	Fetal alcohol syndrome (alcohol exposed) 3433 4433 3434 4434 3443 4443 3444 4444
B	Fetal alcohol syndrome (alcohol exposure unknown) 3432 4432 3442 4442
C	Atypical fetal alcohol syndrome (alcohol exposed) 1443 1434 2434 3334 4334 2443 1444 2444 3344 4344
D	Fetal alcohol syndrome phenocopy (no alcohol exposure) 3431 4341 4441 3441 4431
E	Sentinel physical findings / static encephalopathy (alcohol exposed) 1333 1433 2344 3143 3243 4133 4233 4333 1334 2333 2433 3144 3244 4134 4234 4343 1343 2334 3133 3233 3333 4143 4243 1344 2343 3134 3234 3343 4144 4244
F	Static encephalopathy (alcohol exposed) 1133 1144 1243 2134 2233 2244 1134 1233 1244 2143 2234 1143 1234 2133 2144 2243
G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed) 1323 2323 3123 3323 4123 4323 1324 2324 3124 3324 4124 4324 1423 2423 3223 3423 4223 4423 1424 2424 3224 3424 4224 4424

Category	Diagnostic Name and Codes
H	Neurobehavioral disorder (alcohol exposed)
	1123 2123
	1124 2124
	1223 2223
	1224 2224
I	Sentinel physical findings (alcohol exposed)
	1313 2313 3113 3313 4113 4313
	1314 2314 3114 3314 4114 4314
	1413 2413 3213 3413 4213 4413
	1414 2414 3214 3414 4214 4414
J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)
	1113 2113
	1114 2114
	1213 2213
	1214 2214
K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
	1332 2332 3132 3332 4232
	1342 2342 3142 3342 4242
	1432 2432 3232 4132 4332
	1442 2442 3242 4142 4342
L	Static encephalopathy (alcohol exposure unknown)
	1132 1232 2132 2232
	1142 1242 2142 2242
M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
	1322 2322 3122 3322 4122 4322
	1422 2422 3222 3422 4222 4422
N	Neurobehavioral disorder (alcohol exposure unknown)
	1122 1222 2122 2222
O	Sentinel physical findings (alcohol exposure unknown)
	1312 2312 3112 3312 4112 4312
	1412 2412 3212 3412 4212 4412

Category	Diagnostic Name and Codes
P	No cogn./behavioral or sentinel physical findings detected (alcohol exposure unknown) 1112 2112 1212 2212
Q	Sentinel physical findings / static encephalopathy (no alcohol exposure) 1331 2341 3231 4141 1341 2431 3241 4231 1431 2441 3331 4241 1441 3131 3341 4331 2331 3141 4131
R	Static encephalopathy (no alcohol exposure) 1131 2131 1141 2141 1231 2231 1241 2241
S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure) 1321 3121 4121 1421 3221 4221 2321 3321 4321 2421 3421 4421
T	Neurobehavioral disorder (no alcohol exposure) 1121 2121 2221 1221
U	Sentinel physical findings (no alcohol exposure) 1311 3111 4111 1411 3211 4211 2311 3311 4311 2411 3411 4411
V	No cognitive/behavioral or sentinel physical findings detected (no alcohol exposure) 1111 2111 1211 2211

VI. 4-Digit Diagnostic Codes
Sorted Numerically

Code	Category	Diagnostic Name
1111	V	No cognitive/behavioral or sentinel physical findings detected (no alcohol exposure)
1112	P	No cognitive/behavioral or sentinel physical findings detected (alcohol exposure unknown)
1113	J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)
1114	J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)
1121	T	Neurobehavioral disorder (no alcohol exposure)
1122	N	Neurobehavioral disorder (alcohol exposure unknown)
1123	H	Neurobehavioral disorder (alcohol exposed)
1124	H	Neurobehavioral disorder (alcohol exposed)
1131	R	Static encephalopathy (no alcohol exposure)
1132	L	Static encephalopathy (alcohol exposure unknown)
1133	F	Static encephalopathy (alcohol exposed)
1134	F	Static encephalopathy (alcohol exposed)
1141	R	Static encephalopathy (no alcohol exposure)
1142	L	Static encephalopathy (alcohol exposure unknown)
1143	F	Static encephalopathy (alcohol exposed)
1144	F	Static encephalopathy (alcohol exposed)
1211	V	No cognitive/behavioral or sentinel physical findings detected (no alcohol exposure)
1212	P	No cognitive/behavioral or sentinel physical findings detected (alcohol exposure unknown)
1213	J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)
1214	J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)
1221	T	Neurobehavioral disorder (no alcohol exposure)
1222	N	Neurobehavioral disorder (alcohol exposure unknown)
1223	H	Neurobehavioral disorder (alcohol exposed)
1224	H	Neurobehavioral disorder (alcohol exposed)
1231	R	Static encephalopathy (no alcohol exposure)
1232	L	Static encephalopathy (alcohol exposure unknown)
1233	F	Static encephalopathy (alcohol exposed)
1234	F	Static encephalopathy (alcohol exposed)
1241	R	Static encephalopathy (no alcohol exposure)
1242	L	Static encephalopathy (alcohol exposure unknown)
1243	F	Static encephalopathy (alcohol exposed)
1244	F	Static encephalopathy (alcohol exposed)
1311	U	Sentinel physical findings (no alcohol exposure)
1312	O	Sentinel physical findings (alcohol exposure unknown)
1313	I	Sentinel physical findings (alcohol exposed)
1314	I	Sentinel physical findings (alcohol exposed)
1321	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
1322	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
1323	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)

Code	Category	Diagnostic Name
1324	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
1331	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
1332	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
1333	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
1334	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
1341	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
1342	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
1343	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
1344	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
1411	U	Sentinel physical findings (no alcohol exposure)
1412	O	Sentinel physical findings (alcohol exposure unknown)
1413	I	Sentinel physical findings (alcohol exposed)
1414	I	Sentinel physical findings (alcohol exposed)
1421	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
1422	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
1423	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
1424	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
1431	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
1432	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
1433	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
1434	C	Atypical fetal alcohol syndrome (alcohol exposed)
1441	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
1442	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
1443	C	Atypical fetal alcohol syndrome (alcohol exposed)
1444	C	Atypical fetal alcohol syndrome (alcohol exposed)
2111	V	No cognitive/behavioral or sentinel physical findings detected (no alcohol exposure)
2112	P	No cognitive/behavioral or sentinel physical findings detected (alcohol exposure unknown)
2113	J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)
2114	J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)
2121	T	Neurobehavioral disorder (no alcohol exposure)
2122	N	Neurobehavioral disorder (alcohol exposure unknown)
2123	H	Neurobehavioral disorder (alcohol exposed)
2124	H	Neurobehavioral disorder (alcohol exposed)
2131	R	Static encephalopathy (no alcohol exposure)
2132	L	Static encephalopathy (alcohol exposure unknown)
2133	F	Static encephalopathy (alcohol exposed)
2134	F	Static encephalopathy (alcohol exposed)
2141	R	Static encephalopathy (no alcohol exposure)
2142	L	Static encephalopathy (alcohol exposure unknown)
2143	F	Static encephalopathy (alcohol exposed)
2144	F	Static encephalopathy (alcohol exposed)
2211	V	No cognitive/behavioral or sentinel physical findings detected (no alcohol exposure)
2212	P	No cognitive/behavioral or sentinel physical findings detected (alcohol exposure unknown)
2213	J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)

Code	Category	Diagnostic Name
2214	J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)
2221	T	Neurobehavioral disorder (no alcohol exposure)
2222	N	Neurobehavioral disorder (alcohol exposure unknown)
2223	H	Neurobehavioral disorder (alcohol exposed)
2224	H	Neurobehavioral disorder (alcohol exposed)
2231	R	Static encephalopathy (no alcohol exposure)
2232	L	Static encephalopathy (alcohol exposure unknown)
2233	F	Static encephalopathy (alcohol exposed)
2234	F	Static encephalopathy (alcohol exposed)
2241	R	Static encephalopathy (no alcohol exposure)
2242	L	Static encephalopathy (alcohol exposure unknown)
2243	F	Static encephalopathy (alcohol exposed)
2244	F	Static encephalopathy (alcohol exposed)
2311	U	Sentinel physical findings (no alcohol exposure)
2312	O	Sentinel physical findings (alcohol exposure unknown)
2313	I	Sentinel physical findings (alcohol exposed)
2314	I	Sentinel physical findings (alcohol exposed)
2321	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
2322	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
2323	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
2324	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
2331	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
2332	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
2333	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
2334	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
2341	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
2342	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
2343	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
2344	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
2411	U	Sentinel physical findings (no alcohol exposure)
2412	O	Sentinel physical findings (alcohol exposure unknown)
2413	I	Sentinel physical findings (alcohol exposed)
2414	I	Sentinel physical findings (alcohol exposed)
2421	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
2422	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
2423	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
2424	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
2431	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
2432	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
2433	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
2434	C	Atypical fetal alcohol syndrome (alcohol exposed)
2441	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
2442	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
2443	C	Atypical fetal alcohol syndrome (alcohol exposed)

Code	Category	Diagnostic Name
2444	C	Atypical fetal alcohol syndrome (alcohol exposed)
3111	U	Sentinel physical findings (no alcohol exposure)
3112	O	Sentinel physical findings (alcohol exposure unknown)
3113	I	Sentinel physical findings (alcohol exposed)
3114	I	Sentinel physical findings (alcohol exposed)
3121	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
3122	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
3123	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
3124	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
3131	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
3132	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
3133	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
3134	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
3141	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
3142	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
3143	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
3144	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
3211	U	Sentinel physical findings (no alcohol exposure)
3212	O	Sentinel physical findings (alcohol exposure unknown)
3213	I	Sentinel physical findings (alcohol exposed)
3214	I	Sentinel physical findings (alcohol exposed)
3221	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
3222	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
3223	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
3224	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
3231	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
3232	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
3233	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
3234	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
3241	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
3242	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
3243	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
3244	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
3311	U	Sentinel physical findings (no alcohol exposure)
3312	O	Sentinel physical findings (alcohol exposure unknown)
3313	I	Sentinel physical findings (alcohol exposed)
3314	I	Sentinel physical findings (alcohol exposed)
3321	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
3322	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
3323	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
3324	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
3331	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
3332	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
3333	E	Sentinel physical findings / static encephalopathy (alcohol exposed)

Code	Category	Diagnostic Name
3334	C	Atypical fetal alcohol syndrome (alcohol exposed)
3341	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
3342	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
3343	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
3344	C	Atypical fetal alcohol syndrome (alcohol exposed)
3411	U	Sentinel physical findings (no alcohol exposure)
3412	O	Sentinel physical findings (alcohol exposure unknown)
3413	I	Sentinel physical findings (alcohol exposed)
3414	I	Sentinel physical findings (alcohol exposed)
3421	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
3422	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
3423	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
3424	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
3431	D	Fetal alcohol syndrome phenocopy (no alcohol exposure)
3432	B	Fetal alcohol syndrome (alcohol exposure unknown)
3433	A	Fetal alcohol syndrome (alcohol exposed)
3434	A	Fetal alcohol syndrome (alcohol exposed)
3441	D	Fetal alcohol syndrome phenocopy (no alcohol exposure)
3442	B	Fetal alcohol syndrome (alcohol exposure unknown)
3443	A	Fetal alcohol syndrome (alcohol exposed)
3444	A	Fetal alcohol syndrome (alcohol exposed)
4111	U	Sentinel physical findings (no alcohol exposure)
4112	O	Sentinel physical findings (alcohol exposure unknown)
4113	I	Sentinel physical findings (alcohol exposed)
4114	I	Sentinel physical findings (alcohol exposed)
4121	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
4122	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
4123	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
4124	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
4131	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
4132	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
4133	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
4134	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
4141	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
4142	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
4143	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
4144	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
4211	U	Sentinel physical findings (no alcohol exposure)
4212	O	Sentinel physical findings (alcohol exposure unknown)
4213	I	Sentinel physical findings (alcohol exposed)
4214	I	Sentinel physical findings (alcohol exposed)
4221	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
4222	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
4223	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
4224	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)

Code	Category	Diagnostic Name
4231	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
4232	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
4233	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
4234	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
4241	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
4242	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
4243	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
4244	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
4311	U	Sentinel physical findings (no alcohol exposure)
4312	O	Sentinel physical findings (alcohol exposure unknown)
4313	I	Sentinel physical findings (alcohol exposed)
4314	I	Sentinel physical findings (alcohol exposed)
4321	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
4322	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
4323	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
4324	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
4331	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
4332	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
4333	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
4334	C	Atypical fetal alcohol syndrome (alcohol exposed)
4341	D	Fetal alcohol syndrome phenocopy (no alcohol exposure)
4342	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
4343	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
4344	C	Atypical fetal alcohol syndrome (alcohol exposed)
4411	U	Sentinel physical findings (no alcohol exposure)
4412	O	Sentinel physical findings (alcohol exposure unknown)
4413	I	Sentinel physical findings (alcohol exposed)
4414	I	Sentinel physical findings (alcohol exposed)
4421	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
4422	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
4423	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
4424	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
4431	D	Fetal alcohol syndrome phenocopy (no alcohol exposure)
4432	B	Fetal alcohol syndrome (alcohol exposure unknown)
4433	A	Fetal alcohol syndrome (alcohol exposed)
4434	A	Fetal alcohol syndrome (alcohol exposed)
4441	D	Fetal alcohol syndrome phenocopy (no alcohol exposure)
4442	B	Fetal alcohol syndrome (alcohol exposure unknown)
4443	A	Fetal alcohol syndrome (alcohol exposed)
4444	A	Fetal alcohol syndrome (alcohol exposed)

VII. Clinical Summaries
For each of the 22 Diagnostic Categories

Clinical summaries for each of the 22 Diagnostic Categories are presented on the following pages listed alphabetically from A through V. A complete list of the 22 categories is presented in Section IV.

These summaries can be used as the first page of the final diagnostic report. They often require minor alterations or additions to conform to the specifics of an individual case.

A

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Fetal Alcohol Syndrome**
(2) Alcohol exposed

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of organic brain damage which occur in individuals exposed to alcohol during gestation. On the attached sheets are the specific findings in this patient's case which led to our conclusion that there was sufficient evidence to make the diagnosis of fetal alcohol syndrome.

Although we believe that the patient clearly has fetal alcohol syndrome, this does not mean that alcohol exposure during pregnancy is the only cause of the patient's current problems. A number of other factors could be contributing to the present situation, such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. Such factors may partly explain why there is so much variability in the kinds of specific difficulties that patients with FAS have.

Individuals with FAS have organic brain damage as a major component of their cognitive and behavioral problems and should be viewed individuals with disabilities. The fetal alcohol syndrome diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific concerns that have been identified that need attention.

_____ _____
Physician's Signature Date

B

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Fetal Alcohol Syndrome**
(2) Alcohol exposure unknown

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of organic brain damage occurring in patients exposed to alcohol during gestation. On the attached sheets are the specific findings in this patient's case which led to our conclusion that there was sufficient evidence in this case to make a diagnosis of fetal alcohol syndrome even though the history of exposure to alcohol during gestation could not be confirmed.

Although we believe that the patient clearly has fetal alcohol syndrome, this does not mean that alcohol exposure during pregnancy is the only cause of the patient's current problems. A number of other factors could be contributing to the present issues, such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. Such factors may partly explain why there is so much variability in the kinds of specific difficulties that patients with FAS have.

Individuals with FAS have organic brain damage as a major component of their cognitive and behavioral problems and should be viewed individuals with disabilities. The fetal alcohol syndrome diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific concerns that have been identified that need attention.

_____ _____
Physician's Signature Date

C

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Atypical Fetal Alcohol Syndrome**
(2) Alcohol exposed

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of organic brain damage occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS. Indeed, many patients who have been exposed to alcohol show most, but not all, of the classic features of this syndrome. We use the term "atypical fetal alcohol syndrome" when a patient's characteristic features are very close to the classic features of FAS and the alcohol history strongly suggests that alcohol exposure during gestation was at high risk and likely to have played a role in the syndrome. Patients with atypical FAS either have the full set of facial anomalies found with FAS and evidence of organic brain damage, but do not have growth deficiency; or they have growth deficiency and evidence of organic brain damage, and most but not all of the FAS facial features. As you can see from the enclosed list of features found in this patient, the patient meets the criteria for atypical FAS. Patients diagnosed with atypical FAS must have confirmed exposure to high levels of alcohol during gestation.

In addition to gestational exposure to alcohol, a number of other factors could be contributing to the patient's current problems, such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. Such factors may partly explain why there is so much variability in the kinds of specific difficulties that patients with FAS experience.

Patients with atypical FAS have organic brain damage as a major component of their cognitive and behavioral problems and should be viewed as having a disability. The diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific concerns that have been identified that need attention.

_____ _____
Physician's Signature Date

D

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Fetal Alcohol Syndrome Phenocopy**
(2) No alcohol exposure

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of organic brain damage occurring in patients exposed to alcohol during gestation. On the attached sheets are the specific findings in this patient's case which led to our conclusion that the patient has all of the features of FAS. However, there is good reason to believe this patient was not exposed to alcohol during gestation.

Most syndromes can occasionally arise from an alternate cause. Presumably, this is the situation here. A number of other factors could be contributing to the present situation, such as the patient's genetic background and other potential exposures or problems during pregnancy, and various experiences since birth.

Whatever the cause of this patient's syndrome, there is organic brain damage which is a major component of their cognitive and behavioral problems and the patient should be viewed as a person with a disability. The syndrome diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific concerns that have been identified that need attention.

_____ _____
Physician's Signature Date

E

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Static encephalopathy**
(2) Sentinel physical findings
(3) Alcohol exposed

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of organic brain damage in individuals exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, some but not all of the characteristic growth and facial features associated with FAS were present and there was evidence of organic brain damage as you will see noted on the attached pages. There was also a clear history of exposure to significant amounts of alcohol during gestation. In this situation, we use the terms "static encephalopathy" and "sentinel physical findings" to describe the patient's condition. Static encephalopathy literally means non-progressive brain dysfunction. The diagnoses of "static encephalopathy and sentinel physical findings" in the presence of alcohol exposure do not mean that alcohol is the only cause of the problem. A number of other factors could be contributing to the present issues such as the patient's genetic background, other potential exposures or problems during gestation, and various experiences since birth. These kinds of differences may partly explain why there is so much variability in the kinds of specific difficulties that patients with static encephalopathy and alcohol exposure have.

The diagnoses made today are based on the information available at the time of this assessment. If this patient's alcohol exposure was considered "low risk" and new information is uncovered which documents higher exposures; or if the patient's facial features, growth, or neurobehavioral problems were judged "probable" and further growth or development suggest a "definite" problem is present, then reconsideration of the diagnosis of fetal alcohol syndrome would be appropriate. Alternately other birth defect syndromes not related to alcohol exposure may also need reconsideration.

Individuals with static encephalopathy have organic brain damage which is a major component of their cognitive and behavioral problems and they should be viewed as individuals with disabilities. The static encephalopathy diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

F

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Static Encephalopathy**
(2) Alcohol exposed

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of organic brain damage occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, no growth deficiency or characteristic set of facial features were found so the patient does not have FAS, but there was evidence of organic brain damage as you will see noted on the attached pages. There was also a clear history of exposure to significant amounts of alcohol during gestation. In this situation, we use the term "static encephalopathy" to describe the patient's condition. Static encephalopathy literally means non-progressive brain dysfunction. On the attached sheets are the specific findings in this patient's case which led us to this conclusion. The diagnosis of static encephalopathy does not mean that alcohol is the only cause of the problem. A number of other factors could be contributing to the present issues such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. These kinds of differences may partly explain why there is so much variability in the kinds of specific difficulties that patients with static encephalopathy face.

Individuals with static encephalopathy have organic brain damage which is a major component of their cognitive and behavioral problems and they should be viewed as individuals with disabilities. The static encephalopathy diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

G

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Neurobehavioral disorder**
(2) Sentinel physical findings
(3) Alcohol exposed

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of organic brain damage occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS. On the attached sheets you will find our specific observations in this case. We found that some, but not all, of the characteristic physical findings seen in patients with FAS were present. There was not strong evidence that the patient's cognitive/behavioral problems were clearly due to organic brain damage, but there were suggestions that this was the case. In this situation we use the term "neurobehavioral disorder" to emphasize the possibility that the problems may not be entirely due to postnatal experiences. Certainly a number of other factors could be contributing to the patient's condition such as genetic background, other potential exposures or problems during pregnancy, and various experiences since birth.

The diagnoses made today are based on the information at hand. If further testing is done which makes the likelihood of organic brain damage of prenatal cause more likely, then an alternate diagnosis could be considered. Alternately other birth defect syndromes not related to alcohol exposure may also need consideration.

In any event, the diagnosis of neurobehavioral disorder means that issues of abnormal brain structure and brain impairment need to be considered with implications for educational planning, societal expectations, and health. On the attached sheet, you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

H

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Neurobehavioral disorder**
(2) Alcohol exposed

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of organic brain damage in individuals exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

On the attached sheets you will find our specific observations in this case. There was not strong evidence that the patient's cognitive/behavioral problems were clearly due to organic brain damage, but there were suggestions that this was the case. In this situation we use the term "neurobehavioral disorder" to emphasize the possibility that the problems may not be entirely due to postnatal experiences. Certainly a number of other factors could be contributing to the patient's condition such as genetic background, other potential exposures or problems during gestation, and various experiences since birth.

The diagnosis made today is based on the information available at the time of this assessment. If this patient's alcohol exposure was considered "low risk" and new information is uncovered which documents higher exposure, or if the patient's facial features or growth become more abnormal or if further testing finds further evidence of organic brain damage, then further diagnostic consideration would be appropriate.

Whatever the cause, the diagnosis of neurobehavioral disorder means that issues of abnormal brain structure and brain impairment need to be considered with implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

I

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Sentinel physical findings**
(2) Alcohol exposed

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of organic brain damage occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS. Some individuals have the growth deficiency and/or facial characteristics, but do not have evidence of organic brain damage. We refer to this condition as "Sentinel physical findings / Alcohol exposed". On the attached sheets are the specific findings in this patient's case which indicate that the characteristic growth deficiencies and/or facial features are, to some extent, compatible with FAS, but at this time there is no clear evidence of cognitive or behavioral problems that strongly suggest organic brain damage. At such time in the future that organic brain damage is found through images of the brain, neurologic testing or cognitive behavioral assessment, then the diagnosis of fetal alcohol syndrome should be reconsidered. Other birth defect syndromes that are not related to alcohol exposure should also be considered as alternate explanations for the patient's problems.

_____ _____
Physician's Signature Date

J

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis **(1) No cognitive/behavioral or sentinel physical findings detected**
(2) Alcohol exposed

In this current assessment, we conclude that this patient was exposed to alcohol during gestation, but no specific cognitive, behavioral, or characteristic physical findings were detected in our examination.

No alcohol related diagnoses are offered at this time. Re-evaluation would be appropriate in the future if problems arise that strongly suggested organic brain damage, growth deficiency, or facial dysmorphology.

_____ _____
Physician's Signature Date

K

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis
(1) Static encephalopathy
(2) Sentinel physical findings
(3) Alcohol exposure unknown

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of organic brain damage in individuals exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, some but not all of the characteristic growth and facial features associated with FAS were present and there was evidence of organic brain damage as you will see noted on the attached pages. In this situation, we use the terms "static encephalopathy" and "sentinel physical findings" to describe the patient's condition. Static encephalopathy literally means non-progressive brain dysfunction. Although it is unknown whether this patient was exposed to alcohol during gestation, a number of other factors could be contributing to the patient's current cognitive/behavioral problems such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. These kinds of differences may partly explain why there is so much variability in the kinds of specific difficulties that patients with static encephalopathy have.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal, then further diagnostic consideration would be appropriate. Alternately other birth defect syndromes not related to alcohol exposure may also need reconsideration.

Individuals with static encephalopathy have organic brain damage which is a major component of their cognitive and behavioral problems and they should be viewed as a person with a disability. The static encephalopathy diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

L

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Static encephalopathy**
(2) Alcohol exposure unknown

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of organic brain damage occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, no growth deficiency or characteristic set of facial features were found so the patient does not have FAS, but there was evidence of organic brain damage as you will see noted on the attached pages. In this situation, we use the term "static encephalopathy" to describe the patient's condition. Static encephalopathy literally means non-progressive brain dysfunction. On the attached sheets are the specific findings in this patient's case which led us to this conclusion. Although it is unknown whether this patient was exposed to alcohol during gestation, a number of other factors could be contributing to the patient's current cognitive/behavioral problems such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. These kinds of differences may partly explain why there is so much variability in the kinds of specific difficulties that patients with static encephalopathy face.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal, then further diagnostic consideration would be appropriate.

Individuals with static encephalopathy have organic brain damage which is a major component of their cognitive and behavioral problems and they should be viewed as individuals with disabilities. The static encephalopathy diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

M

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Neurobehavioral disorder**
(2) Sentinel physical findings
(3) Alcohol exposure unknown

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of organic brain damage occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS. On the attached sheets you will find our specific observations in this case. We found that some, but not all, of the characteristic physical findings seen in patients with FAS were present and a confirmed history of alcohol exposure during gestation was not available. There was not strong evidence that the patient's cognitive/behavioral problems were clearly due to organic brain damage, but there were suggestions that this was the case. In this situation we use the term "neurobehavioral disorder" to emphasize the possibility that the problems may not be entirely due to postnatal experiences. Certainly a number of other factors could be contributing to the patient's condition such as genetic background, other potential exposures or problems during pregnancy, and various experiences since birth.

The diagnoses made today are based on the information at hand. If further testing is done which makes the likelihood of organic brain damage of prenatal cause more likely, then an alternate diagnosis would be considered. . Alternately other birth defect syndromes not related to alcohol exposure may also need reconsideration.

In any event, the diagnosis of neurobehavioral disorder means that issues of abnormal brain structure and brain impairment need to be considered with implications for educational planning, societal expectations, and health. On the attached sheet, you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

N

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Neurobehavioral disorder**
(2) Alcohol exposure unknown

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of organic brain damage in individuals exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

On the attached sheets you will find our specific observations in this case. There was not strong evidence that the patient's cognitive/behavioral problems were clearly due to organic brain damage, but there were suggestions that this was the case. In this situation we use the term "neurobehavioral disorder" to emphasize the possibility that the problems may not be entirely due to postnatal experiences. Certainly a number of other factors could be contributing to the patient's condition such as genetic background, other potential exposures or problems during gestation, and various experiences since birth.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal or if further testing finds further evidence of organic brain damage, then further diagnostic consideration would be appropriate.

Whatever the cause, the diagnosis of neurobehavioral disorder means that issues of abnormal brain structure and brain impairment need to be considered with implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____

Physician's Signature Date

O

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Sentinel physical findings**
(2) Alcohol exposure unknown

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of organic brain damage occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

Some individuals have the growth deficiency and/or facial characteristics, but do not have evidence of organic brain damage. We refer to this condition as "Sentinel physical findings". On the attached sheets are the specific findings in this patient's case which indicate that the characteristic growth deficiencies and/or facial features are, to some extent, compatible with FAS, but alcohol exposure during gestation is unknown and at this time there is no clear evidence of cognitive or behavioral problems that strongly suggest organic brain damage. At such time in the future that organic brain damage is found through images of the brain, neurologic testing or cognitive behavioral assessment, and a confirmed history of alcohol exposure is obtained, then further diagnostic consideration would be appropriate. Alternately other birth defect syndromes not related to alcohol exposure may also need reconsideration.

_____ _____
Physician's Signature Date

P

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis **(1) No cognitive/behavioral or sentinel physical findings detected**
(2) Alcohol exposure unknown

In this current assessment, it is unknown whether or not this patient was exposed to alcohol during gestation. Furthermore, no specific cognitive, behavioral, or characteristic physical findings were detected in our examination.

No alcohol related diagnoses are offered at this time. Re-evaluation would be appropriate in the future if further history of alcohol use in pregnancy is documented or problems arise that strongly suggested organic brain damage, growth deficiency, or facial dysmorphology.

_____ _____
Physician's Signature Date

Q

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis
(1) Static encephalopathy
(2) Sentinel physical findings
(3) No alcohol exposure

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of organic brain damage in individuals exposed to alcohol during gestation.

In this patient's case, some but not all of the characteristic growth and facial features associated with FAS were present, there was evidence of organic brain damage, and the patient was reportedly not exposed to alcohol during gestation. Based on these observations, which are documented on the attached pages, this patient does not have FAS, but does have static encephalopathy and some of the physical characteristics found after alcohol exposure. Static encephalopathy literally means non-progressive brain dysfunction. A number of factors other than alcohol could be contributing to the patient's current cognitive/behavioral problems such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. The physical findings may suggest that other syndrome diagnoses be considered.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal, then further diagnostic consideration would be appropriate. . Alternately other birth defect syndromes not related to alcohol exposure may also need reconsideration.

Individuals with static encephalopathy have organic brain damage which is a major component of their cognitive and behavioral problems and they should be viewed as a person with a disability. The static encephalopathy diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

R

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Static encephalopathy**
(2) No alcohol exposure

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of organic brain damage occurring in patients exposed to alcohol during gestation.

In this patient's case, no growth deficiency or characteristic set of facial features were found and the patient was not exposed to alcohol during gestation so the patient does not have FAS, but there was evidence of organic brain damage as you will see noted on the attached pages. In this situation, we use the term "static encephalopathy" to describe the patient's condition. Static encephalopathy literally means non-progressive brain dysfunction. On the attached sheets are the specific findings in this patient's case which led us to this conclusion. A number of factors could be contributing to the patient's current cognitive/behavioral problems such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal, then further diagnostic consideration would be appropriate. . Alternately other birth defect syndromes not related to alcohol exposure may also need reconsideration.

Individuals with static encephalopathy have organic brain damage which is a major component of their cognitive and behavioral problems and they should be viewed as individuals with disabilities. The static encephalopathy diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

S

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis
(1) Neurobehavioral disorder
(2) Sentinel physical findings
(3) No alcohol exposure

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of organic brain damage occurring in patients exposed to alcohol during gestation.

On the attached sheets you will find our specific observations in this case. We found that some, but not all, of the sentinel physical findings seen in patients with FAS were present and the patient was reportedly not exposed to alcohol during gestation. There was not strong evidence that the patient's cognitive/behavioral problems were clearly due to organic brain damage, but there were suggestions that this may be the case. In this situation we use the term "neurobehavioral disorder" to emphasize the possibility that the problems may not be entirely due to postnatal experiences. The patient also had some of the physical characteristics often found with alcohol exposure. In this case, however, there was no alcohol exposure, therefore, these physical findings might suggest that other syndrome diagnoses be considered. Certainly a number of factors could be contributing to the patient's condition such as genetic background, other potential exposures or problems during pregnancy, and various experiences since birth.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal or if further testing finds further evidence of organic brain damage, then further diagnostic consideration would be appropriate.

In any event, the diagnosis of neurobehavioral disorder means that issues of abnormal brain structure and brain impairment need to be considered with implications for educational planning, societal expectations, and health. On the attached sheet, you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

T

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Neurobehavioral disorder**
(2) No alcohol exposure

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of organic brain damage in individuals exposed to alcohol during gestation.

On the attached sheets you will find our specific observations in this case. In this patient's case, no growth deficiency or characteristic set of facial features were found and the patient was not exposed to alcohol during gestation so the patient does not have FAS. Although there was not strong evidence that the patient's cognitive/behavioral problems were clearly due to organic brain damage, there were suggestions that this may be the case. In this situation we use the term "neurobehavioral disorder" to emphasize the possibility that the problems may not be entirely due to postnatal experiences. Certainly a number of other factors could be contributing to the patient's condition such as genetic background, other potential exposures or problems during gestation, and various experiences since birth.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal or if further testing finds further evidence of organic brain damage, then further diagnostic consideration would be appropriate. Alternately other birth defect syndromes not related to alcohol exposure may also need reconsideration.

Whatever the cause, the diagnosis of neurobehavioral disorder means that issues of abnormal brain structure and brain impairment need to be considered with implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

U

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Sentinel physical findings**
(2) No alcohol exposure

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of organic brain damage occurring in patients exposed to alcohol during gestation.

On the attached sheets are the specific findings in this patient's case which indicate that characteristic growth deficiencies and/or facial features, compatible with FAS, were present even though the patient was not exposed to alcohol during gestation. In this case, these physical findings might suggest that other syndrome diagnoses be considered.

At such time in the future that organic brain damage is found through images of the brain, neurologic testing or cognitive behavioral assessment, and/or a confirmed history of alcohol exposure is obtained, then further diagnostic consideration would be appropriate. Alternately other birth defect syndromes not related to alcohol exposure may also need reconsideration.

_____ _____

Physician's Signature Date

V

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis **(1) No cognitive/behavioral or sentinel physical findings detected**
(2) No alcohol exposure

In this current assessment, we conclude that this patient was not exposed to alcohol during gestation. Furthermore, no specific cognitive, behavioral, or characteristic physical findings were detected in our examination.

No diagnoses are offered at this time. Re-evaluation would be appropriate in the future if further history of alcohol use in pregnancy is documented or problems arise that strongly suggested organic brain damage, growth deficiency, or facial dysmorphology.

_____ _____
Physician's Signature Date

VIII. Reference Charts of Normal Growth

The attached charts should be used to record standardized measures of palpebral fissure length, inner canthal distance, head circumference, height, weight, and parental height adjustment on the FAS Diagnostic Evaluation Form.

Palpebral Fissure Distance

(From Hall et. al., 1989, by permission)

eye illustration here Fig 7.43

Measure from the inner to the outer canthi.

Have patient look up while holding head level to standardize and maximize fissure length.

gestational age here Fig 7.44

Palpebral fissure length, both sexes, at birth.

0 to 16 here Fig 7.45

Palpebral fissure length, both sexes, birth to 16 years.

Inner Canthal Distance

(From Hall et. al., 1989, by permission)

eye illustration here Fig 7.32

Measure from the innermost corner of each eye, in a straight line avoiding the curvature of the nose.

gestational age here Fig 7.33

Inner canthal distance, both sexes, at birth.

0 to 16 here Fig 7.34

Inner canthal distance, both sexes, birth to 16 years.

Birth Weight

(Hall et. al., 1989, by permission)

Fig 5.4

North European males at birth

Fig 5.5

North European females at birth

Birth Length

(Hall et. al., 1989, by permission)

Place Fig 4.2 here

Length at birth, North Americans, both sexes.

Birth Length, Twin

(Hall et. al., 1989, by permission)

Place Fig 4.3 here

Twin length at birth, both sexes.

Head Circumference

(Hall et. al., 1989, by permission)

Place Fig. 6.2 here

Head circumference, both sexes, at birth.

Head Circumference BOYS

(Mead Johnson Nutritionals by permission)

Head Circumference GIRLS

(Mead Johnson Nutritionals by permission)

Girls: Birth to 36 Months, Height and Weight, NCHS Percentiles

(Ross Products Division by permission)

Girls: Birth to 36 Months, Head Circumference, NCHS Percentiles

(Ross Products Division by permission)

Girls: 2 to 18 Years, Height and Weight, NCHS Percentiles

(Ross Products Division by permission)

Girls: Prepubesent, Stature to Weight, NCHS Percentiles

(Ross Products Division by permission)

Boys: Birth to 36 Months, Height and Weight, NCHS Percentiles

(Ross Products Division by permission)

Boys: Birth to 36 Months, Head Circumference, NCHS Percentiles

(Ross Products Division by permission)

Boys: 2 to 18 Years, Height and Weight, NCHS Percentiles

(Ross Products Division by permission)

Boys: Prepubescent, Stature to Weight, NCHS Percentiles

(Ross Products Division by permission)

Parent Specific Adjustments for Evaluation of Length and Stature

(Ross Laboratories by permission)

Place Table 1 here

Metric Equivalents (cm) for Length and Stature

Parent Specific Adjustments for Evaluation of Length and Stature (continued)

Instructions

Place Instructions here

Parent Specific Adjustments for Evaluation of Length and Stature (continued)

Boys from Birth to 36 Months

Place Parent-Specific Adjustments for Length of Boys
Birth to 36 Months
Here

Parent Specific Adjustments for Evaluation of Length and Stature (continued)

Boys from 3 to 18 Years

Place Parent-Specific Adjustments for Stature of Boys

2 to 18 Years

Here

Parent Specific Adjustments for Evaluation of Length and Stature (continued)
Girls from Birth to 36 Months

Place Parent-Specific Adjustments for Length of Girls
Birth to 36 Months
Here

Parent Specific Adjustments for Evaluation of Length and Stature (continued)

Girls from 3 to 18 Years

Place Parent-Specific Adjustments for Stature of Girls

2 to 18 Years

Here

IX. Citations

1. Astley SJ, Clarren SK, A case definition and photographic screening tool for the facial phenotype of fetal alcohol syndrome. J. Pediatrics 1996;129:33-41.

2. Farkas, Leslie. Anthropometry of the Head and Face. 2nd edition. Raven Press, New York, pp.405, 1994.

3. Hall JG, Froster-Iskenius UG, Allanson JE. Handbook of Normal Physical Measurements. Oxford University Press, pp. 504, 1989.

4. Nellhaus G., Composite International & Interracial Graphs, Pediatrics 1988;41:106. Head Circumference, Girls and Boys, Birth to 18 Years, Distributed free by Mead Johnson & Company.

5. Ross Laboratories. Ross Growth & Development Program. Parent-Specific Adjustments for Evaluation of Length and Stature- Boys and Girls, 1983, Ross Products Division, Abbott Laboratories, Columbus Ohio, 43216.

6. Ross Laboratories. Birth to 36 Months Physical Growth NCHS Percentiles, Boys and Girls, 1992, Ross Products Division, Abbott Laboratories, Columbus Ohio, 43216.

7. Ross Laboratories. 2 to 18 Years Physical Growth NCHS Percentiles, Boys and Girls, 1994, Ross Products Division, Abbott Laboratories, Columbus Ohio, 43216.

X. Appendix

1. New Patient Information Form

Quick Reference Sheet

GROWTH

Table 1: Deriving the ABC Summary Score

ABC Rank	Centile Range	Circle the ABC-ScoreS for: Height	Weight
C	≤ 3rd	C	C
B	>3rd and ≤ 10th	B	B
A	>10th	A	A

Table 2: Converting the ABC-Score to a 4-Digit Diagnostic Code Rank

4-Digit Diagnostic Code Rank	Growth Deficiency Category	Height-Weight ABC-Score Combinations
4	Severe	CC
3	Moderate	CB, BC
2	Mild	CA, BB, AC
1	None	BA, AB, AA

FACE

Table 3: Deriving the ABC Summary Score

5-Point Likert Scale for Philtrum & Lip	Standard Deviation Scale for Fissures	Circle the ABC-Scores for: Palpebral Fissures	Smooth Philtrum	Thin Upper Lip
4 or 5	≤ -2 SD	C	C	C
3	>-2 SD and ≤ -1 SD	B	B	B
1 or 2	> -1 SD	A	A	A

Table 4: Converting the ABC-Score to a 4-Digit Diagnostic Code Rank

4-Digit Diagnostic Code Rank	Level of Expression of the FAS Facial Features	Palpebral Fissure - Philtrum - Lip ABC-Score Combinations
4	Severe	CCC
3	Moderate	CCB, CBC, BCC
2	Mild	CCA, CAC, CBB, CBA, CAB, CAA, BCB, BCA, BBC, BAC ACC, ACB, ACA, ABC, AAC
1	Absent	BBB, BBA, BAB, BAA ABB, ABA, AAB, AAA

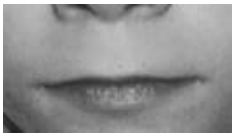
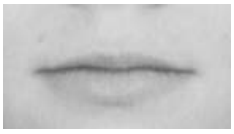
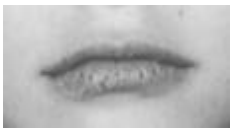
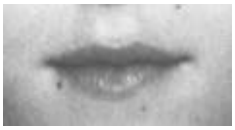
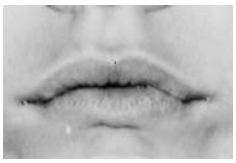
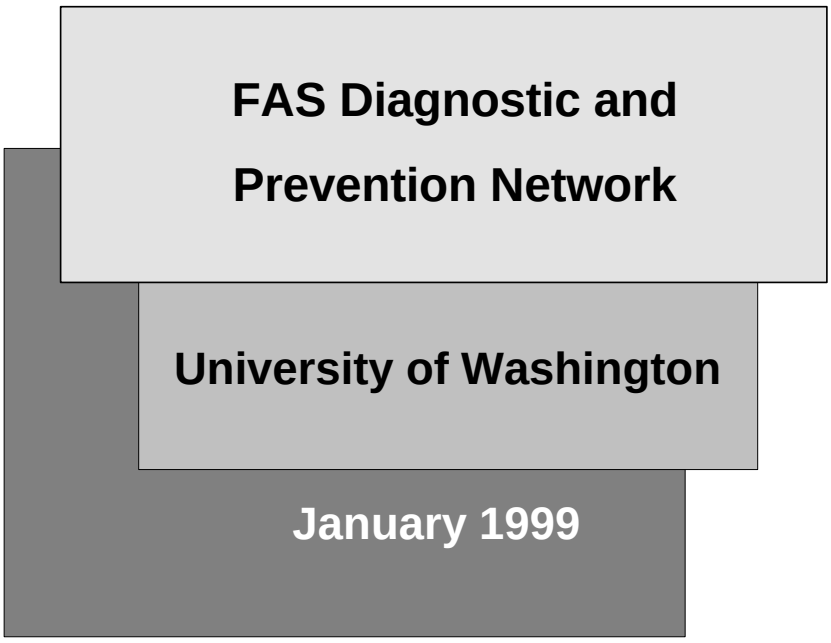
Philtrum/Upper Lip	Philtrum Likert Scale	Upper Lip Likert Scale	ABC Scale
	5	5	C
	4	4	C
	3	3	B
	2	2	A
	1	1	A

Figure 1. Pictorial examples of the 5-point Likert scales and the ABC scale used to rank upper lip thinness and philtrum smoothness. It is important that the individual's lips are gently closed.

Diagnostic Guide for Fetal Alcohol Syndrome and Related Conditions

The 4-Digit Diagnostic Code

Second Edition



Diagnostic Guide for Fetal Alcohol Syndrome and Related Conditions: The 4-Digit Diagnostic Code, 2nd Edition 1999.

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Contents

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Preface

This Diagnostic Guide is the second edition. Based on our own experience and feedback from others, we continue to make modifications that enhance accuracy, improve clarity, and increase ease of usage. We hope you will find this new approach to the diagnosis of individuals with fetal alcohol exposure helpful and broadly applicable.

I. Introduction

Fetal alcohol syndrome (FAS).

FAS is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. The definition of the fetal alcohol syndrome has changed little since the 1970's when the condition was first described and refined [1,2,3,4]. The condition has been broadly characterized by pre- and/or postnatal growth deficiency, a characteristic set of minor facial anomalies, and evidence of prenatal alteration in brain function such as microcephaly from birth, neurologic problems without postnatal antecedents, or complex patterns of functional disability.

The difficulty with diagnosing FAS and other disabilities associated with in utero alcohol exposure.

For the trained clinician, dysmorphologist, or clinical geneticist there is little difficulty in making the diagnosis of FAS when the typical anomalies in growth, face, and brain are all extreme and the alcohol exposure is conclusive and substantial. But the physical, cognitive and behavioral features are not dichotomous, that is either normal or clearly abnormal. Rather, the features, and indeed the history of alcohol exposure, all range along separate continua from normal to clearly abnormal and distinctive.

In the absence of accurate, reproducible and unbiased methods for measuring and recording the severity of exposure and outcome in individual patients, diagnoses will continue to vary widely from clinic to clinic. From a clinical perspective, diagnostic misclassification leads to inappropriate patient care, increased risk for secondary disabilities[5] and missed opportunities to achieve prevention. From a public health perspective, diagnostic misclassification leads to inaccurate estimates of incidence and prevalence. Inaccurate estimates thwart efforts to allocate sufficient social and health care services to this high-risk population and preclude accurate assessment of primary prevention intervention efforts. From a clinical research perspective, diagnostic misclassification reduces the power to identify between-group contrasts within studies. Non-standardized diagnostic methods limit the ability to compare outcomes between studies.

The primary limitations in the current practice of diagnosing individuals with prenatal alcohol exposure include:

1. There is no standardized clinical definition of FAS. Rather, there are diagnostic guidelines that physicians and medical researchers are encouraged to follow, but the guidelines are not sufficiently *specific* to assure diagnostic accuracy or precision.

   According to the latest proposed diagnostic guidelines published by Sokol and Clarren[3] which are a minor modification of the 1980 definition of FAS by the Fetal Alcohol Study Group of the Research Society for Alcoholism [6]:

"The diagnosis of FAS can only be made when the patient has signs of abnormality in each of the three categories: 1) Prenatal and/or postnatal growth retardation (weight and/or length below the 10th percentile when corrected for gestational age), 2) central nervous system involvement (including neurological abnormality, developmental delay, behavioral dysfunction or deficit, intellectual impairment and/or structural abnormalities, such as microcephaly (head circumference below the 3rd percentile) or brain malformations found on imaging studies or autopsy and 3) a characteristic face, currently qualitatively described as including short palpebral fissures, an elongated midface, a long and flattened philtrum, thin upper lip, and flattened maxilla."

Although these descriptions do provide guidance, they are not sufficiently specific to assure diagnostic accuracy and precision. The guidelines for CNS dysfunction do not address how many areas of deficit must be present, how severe the deficits must be or what level of documentation must exist to substantiate the presence of the deficit (i.e., parental history, psychometric testing or structural imaging). The guidelines for the facial phenotype are equally nonspecific. How many facial features must be present, how severe must the features be and what scale of measurement should be used to judge their severity? One need only read the clinical literature or review medical records, birth certificates, birth defect registries or ICD-9 codes to see how variably these criteria are interpreted, applied and reported [7,8,9,10,11].

2. There is a lack of objective, quantitative scales to measure and report the magnitude of expression of key diagnostic features.

   For example, although a thin upper lip and smooth philtrum are key diagnostic features[12], quantitative measurement scales have never been used to measure thinness or smoothness and guidelines have never been established for how thin or smooth the features must be. Objective quantitative scales would not only improve accuracy and precision, but would also establish a common descriptive language for communicating outcomes in medical records and the medical literature.

3. The term FAS fails to convey the diversity of disability present in individuals with FAS.

   No two individuals with FAS present with the same constellation of anomalies and disabilities. Growth, facial phenotype, CNS dysfunction and alcohol exposure all vary along separate continua. The term FAS only conveys that the condition is permanent and was caused by prenatal alcohol exposure. The term does not convey what the individual's disabilities are. A nomenclature that better conveys the diversity of outcomes among individuals with prenatal exposure would benefit both the patient's caregivers and their medical/social/educational care network.

4. The term fetal alcohol effects (FAE) is broadly used and poorly defined.

   The term 'suspected fetal alcohol effects' was first introduced into the medical literature in 1978 and was defined as 'less complete partial expressions' of FAS in individuals with prenatal alcohol exposure[2]. Based on this definition, an individual whose mother drank a few glasses of wine

intermittently throughout pregnancy and presented with attention deficit hyperactivity disorder would be diagnosed FAE. So would an individual whose mother drank a fifth of vodka daily throughout pregnancy and presented with microcephaly, severe mental retardation, cleft palate and severe growth deficiency. The broad use of this term and the reluctance to abandon it points to the clear need to develop diagnostic terms for individuals with prenatal alcohol exposure who present with physical anomalies and/or cognitive/behavioral disabilities, but do not have FAS. New diagnostic terms, which more finely differentiate the variable exposures and outcomes of these individuals without implying alcohol as the sole causal agent, are needed.

5. Clinical terms like FAE[13], alcohol related birth defects (ARBD)[4] and alcohol related neurodevelopmental disorder (ARND)[4] inappropriately imply a causal link between exposure and outcome in a given individual. Leading dysmorphologists in the field of FAS diagnosis have formally requested that the term FAE no longer be used for this reason[13].

   With the likely exception of the facial phenotype, no other physical anomalies or cognitive/behavioral disabilities observed in an individual with prenatal alcohol exposure are necessarily specific to (caused only by) their prenatal alcohol exposure. Features such as microcephaly, neurological abnormalities, attention deficit, mental retardation and growth deficiency often occur in individuals with prenatal alcohol exposure, but also often occur in individuals with no prenatal alcohol exposure.

A new approach to diagnosis.

Each of the above limitations has been overcome with the development the "*4-Digit Diagnostic Code*" introduced in this guide. The four digits reflect the magnitude of expression of four key diagnostic features of FAS in the following order: (1) growth deficiency, (2) the FAS facial phenotype, (3) brain dysfunction, and (4) gestational alcohol exposure. The magnitude of expression of each feature is ranked independently on a 4-point Likert scale with 1 reflecting complete absence of the FAS feature and 4 reflecting a strong "classic" presence of the FAS feature.

Benefits of the new diagnostic approach.

This new approach:

1. Greatly increases diagnostic precision and accuracy through the use of objective, quantitative measurement scales and specific case definitions.

2. Better characterizes the full spectrum of disabilities of alcohol exposed individuals who do and do not have FAS.

3. Documents the presence of alcohol exposure without judging its causal role.

4. Provides a quantitative measurement and reporting system that can be used independent of the clinical case definitions.

While this document might at first appear overly complex and perhaps daunting, one will find that this new diagnostic approach is logical and easy to use and will greatly facilitate the proper description and classification of patients presenting with all possible combinations of outcomes and exposure.

Other syndromes

The methods of diagnosing fetal alcohol syndrome and related conditions arise from the larger fields of teratology and dysmorphology (clinical genetics). It is essential to remember that isolated features in many birth defect syndromes overlap with FAS. A few examples of conditions often easily confused with FAS include Aarskog syndrome, fragile-x syndrome, fetal hydantoin syndrome and Noonan syndrome. Furthermore it is likely that this diagnostic approach to organizing dysmorphic features and issues of cognitive and behavioral problems could be used for patients exposed to other potentially teratogenic substances instead of or in addition to alcohol. This diagnostic guide is "FAS specific" but this in no way should imply that the diagnostician need not consider alternate syndromic diagnoses and medical conditions at all times.

II. FAS Diagnostic Evaluation Form

The FAS Diagnostic Evaluation Form guides the clinical team in the collection, recording, and interpretation of all key information used to derive an accurate and precise diagnosis. Although the most accurate diagnoses are derived when complete information is available across all domains, complete information is not always available or obtainable. This is especially true with psychometric assessments. Although space has been provided to record a full complement of assessments, we are not implying that all of these assessments must be conducted to derive a diagnosis. It is the responsibility of the clinical team to select the most appropriate psychometric assessment battery.

The form also serves as a template for efficient generation of the final medical summary note.

Where is the information for the Diagnostic Form obtained from?

The information recorded in the Diagnostic Form is obtained from four primary sources:

1. The New Patient Information Form completed by the caregivers (Appendix 1).
2. Medical/psychological/educational assessments conducted prior to the diagnostic evaluation.
3. Assessments administered by the clinical staff at the time of the diagnostic evaluation.
4. The caregiver/patient interview conducted at the time of the diagnostic evaluation

When is the form completed and by whom?

The form is completed by the clinical staff before and during the patient's clinic visit. Typically, the clinician completes the following sections: growth, structural and neurologic brain function, facial features, alcohol exposure and co-morbidities. The occupational therapist, psychologist and language pathologist complete the psychometric measures of brain function and the results of the caregiver interview are completed by the clinician and psychologist.

FAS Diagnostic Evaluation Form

Medical # _____ Clinic _____ Date seen in Clinic ___ / ___ / ___

Patient's Name: _____ _____ _____ Age(y) _____ Birth Date ___ / ___ / ___
First Middle Last

Name person(s) accompanying patient _____

Relationship(s) to patient _____ Patient's Gender M F

Patient's Race/Ethnicity: _____

Form completed by: _____

Diagnosis made by: _____

Diagnosis(es): _____

_____

_____

4-Digit Diagnostic Code Grid

(See instructions in Diagnostic Guide for FAS and Related Conditions)

Growth Deficiency	FAS Facial Features	Brain Dysfunction		Growth	Face	Brain	Alcohol		Gestational Alcohol
significant	severe	definite	4					4	high risk
moderate	moderate	probable	3					3	some risk
mild	mild	possible	2					2	unknown
none	absent	unlikely	1					1	no risk

GROWTH

At Birth

Birth weight: _____ (gms) _____ (lbs/oz.), _____ (centile) for gestational age

Birth length _____ (cm) _____ (inches), _____ (centile) for gestational age

Gestational age at birth_____ (weeks)

Highest Weight and Height Centiles Recorded

wgt _____(kg), _____(lbs), _____ (centile), age _____(yr)

hgt _____(cm), _____(inches), _____ (centile), age _____(yr), parent adjustment _____(cm)

Lowest Weight and Height Centiles Recorded

wgt _____(kg), _____(lbs), _____ (centile), age _____(yr)

hgt _____(cm), _____(inches), _____ (centile), age _____(yr), parent adjustment _____(cm)

Current Weight and Height

wgt _____(kg), _____(lbs), _____ (centile), age _____(yr)

hgt _____(cm), _____(inches), _____ (centile), age _____(yr), parent adjustment _____(cm)

Birth Parent's Heights

mother's hgt _____(cm)_____(inches), father's hgt _____(cm)_____(inches), mid-parent hgt _____(cm)

ABC-Score for Growth Deficiency

See instructions in the "Diagnostic Guide for FAS" for deriving the ABC-score for growth and translating it into a 4-Digit Diagnostic Code

Circle the ABC Scores for:

	Height	Weight
≤ 3rd centile = **C**	C	C
>3rd and ≤ 10th centile = **B**	B	B
> 10th centile = **A**	A	A

This ABC Score reflects the patient's growth between _____ years and _____ years of age.

FACIAL FEATURES (and other physical findings)

CURRENT PHENOTYPE: (Age _____ yrs)

Direct measures

Right palpebral fissure length (PFL) _____ (cm) _____ (z-score)

Left palpebral fissure length (PFL) _____ (cm) _____ (z-score)

Inner canthal distance (ICD) _____ (cm) _____ (z-score)

	Not Present		*Mildly Present*		*Definitely Present**	
Flat philtrum·	_____ 1	_____ 2	_____ 3	_____ 4	_____ 5	(*flat*)
Thin upper lip·	_____	_____	_____	_____	_____	(*thin*)

Clinic Photograph **Internal Measure** True size _____ Units (_____)

Was a facial photograph taken? Yes ___, No ___ Size in photo _____ Units (_____)

Right PFL Length in photo _____ (pixels or mm): True estimate _____ (cm) _____ (z-score)

Left PFL Length in photo _____ (pixels or mm): True estimate _____ (cm) _____ (z-score)

ICD Length in photo _____ (pixels or mm): True estimate _____ (cm) _____ (z-score)

	Not Present		*Mildly Present*		*Definitely Present*		Upper Lip
Flat philtrum·	_____ 1	_____ 2	_____ 3	_____ 4	_____ 5	(*flat*)	Circularity··
Thin upper lip·	_____	_____	_____	_____	_____	(*thin*)	_____

PAST PHENOTYPE (Age _____ yrs) **Internal Measure** True size _____ Units (_____)

Source of data (photograph ___, text record ____) Size in photo _____ Units (_____)

Right PFL Length in photo _____ (pixels or mm): True estimate _____ (cm) _____ (z-score)

Left PFL Length in photo _____ (pixels or mm): True estimate _____ (cm) _____ (z-score)

ICD Length in photo _____ (pixels or mm): True estimate _____ (cm) _____ (z-score)

	Not Present		*Mildly Present*		*Definitely Present*		Upper Lip
Flat philtrum·	_____ 1	_____ 2	_____ 3	_____ 4	_____ 5	(*flat*)	Circularity··
Thin upper lip·	_____	_____	_____	_____	_____	(*thin*)	_____

Facial D-score·· _____ Dscore = 0.7408 – 5.7337 (Largest PFL/ICD) + 1.1677 (philtrum Likert rank) + 0.1587 (upper lip Likert rank)

(Use Lip-Philtrum Guide on page 26, Figure 1)* * (See Astley & Clarren, 1996)*

ABC-SCORE for Facial Phenotype

See instructions in the "Diagnostic Guide for FAS" for deriving the ABC Score and translating it into a 4-Digit Diagnostic Code

5-Point Likert Scale for Philtrum & Lip	Z-score for Largest Palpebral Fissure	*Circle the ABC Scores for:* Palpebral Fissure	Smooth Philtrum	Thin Upper Lip
4 or 5	≤ -2 SD	C	C	C
3	>-2 SD and ≤ -1 SD	B	B	B
1 or 2	> -1 SD	A	A	A

ALL ADDITIONAL PHYSICAL ANOMALIES ON THE BODY

_____

_____

BRAIN FUNCTION

Examiner's Clinical Judgment of Severity of Outcome
Circle: 0 = Unable to Judge, 1 = Normal, 2 = Mildly Abnormal, 3 = Severely Abnormal

Severity

STRUCTURAL

0 1 2 3 OFC _____ (cm) _____ (centile) at _____ (years) of age.

0 1 2 3 Structural anomalies on CT/MRI _____

0 1 2 3 Other: _____

NEUROLOGIC

0 1 2 3 Seizure Disorder: type _____ Age at onset _____ (yrs)

0 1 2 3 Gross motor _____

0 1 2 3 Fine motor _____

0 1 2 3 Quick Neurological Screening Test score _____

0 1 2 3 Other neurologic signs _____

PSYCHOMETRIC *Provide most recent test scores*

0 1 2 3 **Intellectual**: (test/version) _____ Age _____ (yr/mos)

FSIQ or equiv. ____ VIQ _____PIQ _____ PercOrg _____ VerbComp _____ FreeDis _____

Inf. ___ Sim. ___ Arith. ___ Voc. ___ Comm. ___ Dig. ___ Pict C. ____ Pict. A. ___ Blo. ___ Obj. ___ Cod. ___ Maz. ___

_____

_____ Age(s) of previous intelligence tests _____ (yrs)

0 1 2 3 **Achievement** (test/version) _____ Age _____ (yr/mos)

Subtest	Score	Type of Score (standard, %, age equiv., T, Z, etc)

Age(s) of previous Achievement tests _____ (yrs)

0 1 2 3 **Adaptation** (test/version) _____ Age _____ (yr/mos)

Composite Score Name	Score	Type of Score (standard, %, age equiv., T, Z, etc)

Subtest		

Age(s) of previous Adaptation tests _____ (yrs)

See the "Diagnostic Guide for FAS" for instructions on deriving the 4-Digit Diagnostic Code for Brain Dysfunction Page 3 of 7

BRAIN FUNCTION (Continued)

Examiner's Clinical Judgment of Severity of Outcome

Circle: 0 = Unable to Judge, 1 = Normal, 2 = Mildly Abnormal, 3 = Severely Abnormal

Severity

0 1 2 3 **Psychiatric Diagnoses:** ADHD / ADD (____ yes, _____no, _____ unknown)

other (*specify*) _____

Medication(s)	Response (+, -, none)	Medication(s)	Response (+, -, none)

0 1 2 3 **Neuropsychological** (e.g., VMI, CVLT-C, Halstead-Reitan, WRAML, Rey, Bender-G, Luria-Nebraska, etc)

Test name	Score	Type of Score (standard, %, age equiv., T, Z, etc)	Age (yr/months)

0 1 2 3 **Language**

Test name	Score	Type of Score (standard, %, age equiv., T, Z, etc)	Age (yr/months)

0 1 2 3 Mental State Reasoning Test [14, 15] Age _____ (yr/mos)

1st Order (Belief _____ Justification _____) 2nd Order (Belief _____Justification _____)

0 1 2 3 Narrative Test [14, 15] Age _____ (yr/mos)

Bus Story _____ Frog Story _____

0 1 2 3 **Developmental** (test/version) _____ Age _____ (yr/mos)

Subtest	Score	Type of Score (standard, %, age equiv., T, Z, etc.)

See the "Diagnostic Guide for FAS" for instructions on deriving the 4-Digit Diagnostic Code for Brain Dysfunction

BRAIN FUNCTION (Continued)

Examiner's Clinical Judgment of Severity of Outcome

Circle: 0 = Unable to Judge, 1 = No, Normal 2 = Yes, Mildly Abnormal, 3 = Yes, Severely Abnormal

Severity

CAREGIVER INTERVIEW *These observations are intended to support, not define, clinical impressions*

Planning

0 1 2 3 Needs considerable help organizing daily tasks
0 1 2 3 Cannot organize time,
0 1 2 3 Doesn't understand concept of time
0 1 2 3 Difficulty in carrying out multi-step tasks
0 1 2 3 Other _____

Behavioral Regulation/ Sensory Motor Integration

0 1 2 3 Poor management of anger / tantrums
0 1 2 3 Mood swings
0 1 2 3 Impulsive
0 1 2 3 Compulsive
0 1 2 3 Perseverative,
0 1 2 3 Inattentive
0 1 2 3 Inappropriately [high or low] activity level
0 1 2 3 Lying/stealing
0 1 2 3 Unusual [high or low] reactivity to [sound touch light]
0 1 2 3 Other _____

Abstract Thinking / Judgment

0 1 2 3 Poor judgment
0 1 2 3 Cannot be left alone
0 1 2 3 Concrete, unable to think abstractly
0 1 2 3 Other _____

Memory / Learning / Information Processing

0 1 2 3 Poor memory, inconsistent retrieval of learned information
0 1 2 3 Slow to learn new skills
0 1 2 3 Does not seem to learn from past experiences
0 1 2 3 Problems recognizing consequences of actions
0 1 2 3 Problems with information processing speed and accuracy
0 1 2 3 Other _____

Spatial Memory

0 1 2 3 Gets lost easily, has difficulty navigating from point A to point B
0 1 2 3 Other _____

Social Skills and Adaptive Behavior

0 1 2 3 Behaves at a level notably younger than chronological age
0 1 2 3 Poor social/adaptive skills
0 1 2 3 Other _____

Motor/Oral Motor Control

0 1 2 3 Poor/delayed motor skills
0 1 2 3 Poor balance
0 1 2 3 Other _____

0 1 2 3 **Behavioral/Social Competence:** (test) _____ Age _____ (yr/mos)

Subtest	Score	Type of Score (standard, %, age equiv., T, Z, etc)

See the "Diagnostic Guide for FAS" for instructions on deriving the 4-Digit Diagnostic Code for Brain Dysfunction

MATERNAL ALCOHOL USE

Alcohol consumption of the birth mother

Before pregnancy: Average number of drinks per drinking occasion: _____

Maximum number of drinks per occasion: _____

Average number of drinking days per week: _____

Type of alcohol consumed ___Wine, ___ Beer, ___ Liquor, ___ Unk., ___ Other *(specify)* _____

During pregnancy: Average number of drinks per drinking occasion: _____

Maximum number of drinks per occasion: _____

Average number of drinking days per week: _____

Type of alcohol consumed ___ Wine, ___ Beer, ___ Liquor, ___ Unk., ___ Other *(specify)* _____

Trimester(s) in which alcohol was consumed ____ 1st ____ 2nd ____ 3rd ____ Unk. ____ None

	No	Suspected	Yes	Unknown
Was the birth mother ever diagnosed with alcoholism?	___	_____	___	_____
Was the birth mother ever reported to have a problem with alcohol?	___	_____	___	_____
Did the birth mother ever receive treatment for alcohol addiction?	___	_____	___	_____
Was alcohol use during this pregnancy positively confirmed?	___	_____	___	_____

If, yes, source of confirmation _____

Reported use of alcohol during pregnancy is: ___ Reliable, ___ Somewhat reliable, ___ Of unknown reliability

Other information about alcohol use during pregnancy: _____

_____

_____

4-DIGIT RANK for Alcohol Exposure

4-Digit Diagnostic Code Rank	Gestational Alcohol Exposure Category	Description
4	High Risk	● Alcohol use during pregnancy CONFIRMED *and* ● Exposure pattern is consistent with the medical literature placing the fetus at "high risk" (generally high peak blood alcohol concentrations delivered at least weekly in early pregnancy).
3	Some Risk	● Alcohol use during pregnancy CONFIRMED *and* ● Drinking occurred in gestation in frequencies and volumes less than in category (4) or exact amounts unknown.
2	Unknown Risk	● Gestational exposure is simply not known or information is of questionable reliability
1	No Risk	● Alcohol use during pregnancy is CONFIRMED to be completely ABSENT.

Circle the 4-Digit Diagnostic Code Rank in the table above that best reflects the patient's gestational Alcohol Exposure Category

CO-MORBIDITIES

PRENATAL

High risk	Some risk	Unknown risk	No risk
4	3	2	1

See the "Diagnostic Guide for FAS" for instructions on deriving the rank for Prenatal Co-morbidities

Prenatal

1. Poor prenatal care: ____ No ____ Suspected ____ Yes ____ Unknown
2. Complications/trauma (specify) _____

Genetics

1. Parental learning difficulties (e.g. Special Ed., ADD, MR, did not complete high school, etc.)

   Mother ____ No ____ Suspected ____ Yes ____ Unknown

   Father ____ No ____ Suspected ____ Yes ____ Unknown

   If yes, specify Maternal _____

   Paternal _____
2. Other conditions of heritability or malformation that may be significant in this case. *(specify)*

   _____

Other Potentially Teratogenic Exposures

_____

_____

POSTNATAL

High risk	Some risk	Unknown risk	No risk
4	3	2	1

See the "Diagnostic Guide for FAS" for instructions on deriving the rank for Postnatal Co-morbidities

Perinatal Difficulties

_____

_____

Issues of Nurture

1. Abuse: Physical _____ Sexual _____
2. Number of home placements _____
3. Other (e.g., neglect, adverse home environment, etc) _____

   _____

   _____

   _____

Other Issues That Could Explain Brain Dysfunction (e.g., head injuries, fever, chronic substance abuse, etc.)

_____

_____

_____

FAS Diagnostic and Prevention Network
Preliminary Summary and Recommendations

The final medical summary will be sent to you in approximately two weeks.

Patient Name: _____ Clinic: _____

Birth Date: _____ / _____ / _____ Clinic Date: ____ / ____ / ____ Clinic phone: _____

Diagnostic Outcome: _____

Result(s) of assessment(s) performed in Clinic (if applicable):

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Recommendations for Follow-Up

A. Medical Issues

_____

_____

_____

_____

_____

_____

_____

FAS Diagnostic and Prevention Network
Preliminary Summary and Recommendations

Patient Name: _____ Birth Date: _____ / _____ / _____

Recommendations for Follow-Up

B. Developmental, Educational, Vocational, Mental Health, and Family Issues

III. Diagnostic Evaluation Form Instructions

A. The 4-Digit Diagnostic Code

What are the 4 Digits?

The four digits reflect the magnitude of expression of the four key diagnostic features of FAS in the following order: (1) growth deficiency, (2) the FAS facial phenotype, (3) brain dysfunction, and (4) gestational alcohol exposure. The 4-Digit Diagnostic Code is generated at the completion of the diagnostic evaluation using information recorded on the FAS Diagnostic Evaluation Form. The code is derived following the directions in Sections III. B. 1 through B. 4.

4-Digit Diagnostic Code Grid

3 4 4 4

Growth Deficiency	FAS Facial Features	Brain Dysfunction		Growth	Face	Brain	Alcohol		Gestational Alcohol
significant	severe	definite	(4)		X	X	X	(4)	high risk
moderate	moderate	probable	(3)	X				(3)	some risk
mild	mild	possible	(2)					(2)	unknown
none	absent	unlikely	(1)					(1)	no risk

The 4-Digit Diagnostic Code 3444 inserted in the grid is one of twelve that qualifies as a diagnosis of FAS.

How are the 4 Digits ranked?

The magnitude of expression of each feature is ranked independently on a 4-point Likert scale with 1 reflecting complete absence of the FAS feature and 4 reflecting a strong "classic" presence of the FAS feature. Specific guidelines for ranking the magnitude of each of the FAS features are presented in Section III.B.

How many 4-Digit Diagnostic Codes are there?

There are 256 possible 4-Digit Diagnostic Codes ranging from 1111 to 4444. The 256 codes and their corresponding clinical names are listed in numerical order in Section VI.

We have created diagnostic categories for all potential codes, even though to date we do not expect to see all of these situations in clinic. For example, 1111 reflects a normal exam in an individual who was definitely not exposed to alcohol. Such patients are seen by primary physicians daily, but are unlikely to be referred to a FAS clinic. Other codes like 4441 would represent a “classic” clinical presentation of FAS with a confirmed absence of alcohol exposure during gestation. We have never seen such a case (or phenocopy), but we may some day.

How many different Clinical Diagnostic Categories are there?

Each 4-Digit Diagnostic Code falls into one of 22 unique Clinical Diagnostic Categories (labeled A through V). A list of the 22 Diagnostic Categories is presented in Section IV. A list of the 4-Digit Diagnostic Codes, which fall within each Clinical Diagnostic Category, is presented in Section V.

What are the names of the Clinical Diagnostic Categories?

The following terms are used in varying combinations to name the 22 diagnostic categories. They include:

- **Sentinel Physical Findings:**
  The adjective *"sentinel"* refers to physical findings that are key diagnostic features of FAS. These include a unique cluster of minor facial anomalies (short palpebral fissures, thin upper lip and a smooth philtrum) and growth deficiency. Other physical findings (major or minor anomalies) may be detected instead of or in addition to these sentinel findings that may suggest alternate or additional conditions. There are places on the Diagnostic Evaluation Form to record and interpret other physical findings.

- **Static Encephalopathy:**
  The term *"encephalopathy"* refers to any physical abnormality in the brain. Such abnormalities can vary in magnitude from structural defects that are apparent on an image like a CT scan to micro-cellular abnormalities that can only be confirmed with tissue samples or neurochemical analysis. The term *"static"* means that the physical abnormality in the brain is unchanging, neither progressing nor regressing. The term *"static encephalopathy"* is used in this diagnostic system when the patient presents with cognitive/behavioral dysfunction which is accompanied by structural, neurologic, and/or psychometric measures which strongly support the presence of structural brain abnormalities. The term does not define or suggest any specific pattern of structural abnormality or cognitive/behavioral dysfunction.

- **Neurobehavioral Disorder:**
  This term is used in this diagnostic system when the patient presents with cognitive/behavioral dysfunction, but structural, neurologic and psychometric measures do not unequivocally support the presence of structural brain abnormalities.

- **Alcohol (Exposed, Not Exposed, Exposure Unknown):**
  This term is used to reflect the exposure status of the fetus. It is reported independent of outcome and does not imply a causal association between exposure and outcome.

- **Fetal Alcohol Syndrome:**
  The term FAS is used to refer to patients who present with one of twelve 4-Digit Diagnostic Code combinations reflecting growth deficiency, the FAS facial phenotype and brain dysfunction.

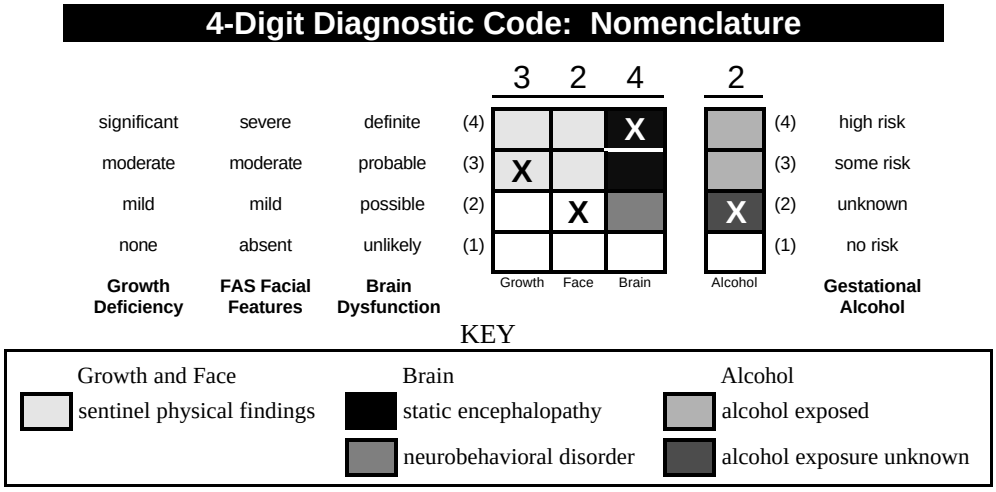
- **Atypical Fetal Alcohol Syndrome:**
  This term is introduced for use with a relatively small group of patients who have static encephalopathy, most of the sentinel physical findings of FAS, and were alcohol exposed. Given the fact that variable presentation is the rule rather than the exception after teratogenic exposure in gestation, we felt it was appropriate to establish this marginal category.

The names assigned to each diagnostic category reflect the patient's clinical outcome and alcohol exposure. The names are listed in Sections IV and V. The first three categories (A through C) meet the criteria for a clinical diagnosis of FAS and are named as such. The fourth category (D) applies to the patient who presents with all of the features of FAS, but has a confirmed *absence* of gestational alcohol exposure. This category is referred to as a FAS Phenocopy and has yet to be observed.

The remaining 19 categories (E through V) do not meet the minimum criteria for FAS and are subsequently named to reflect the Likert ranking of each digit in the 4-Digit Diagnostic Code. For example, a code of 4333 is the Diagnostic Category called "*sentinel physical findings / static encephalopathy (alcohol exposed)*". Many of these patients might have previously been referred to variably as having possible fetal alcohol effects (PFAE), alcohol related birth defects (ARBD), or alcohol related neurodevelopmental disorder (ARND). This new nomenclature supersedes all of these terms.

How are the Clinical Diagnostic Category names constructed?

- Growth deficiency and facial characteristics are physical features. When either feature receives a rank of 3 or 4, *sentinel physical findings* is placed at the beginning of the name.
- When brain dysfunction receives a rank of 2, the term *neurobehavioral disorder* is included in the name. When brain dysfunction receives a rank of 3 or 4, the term *static encephalopathy* is included in the name.
- When alcohol exposure receives a rank of 3 or 4, (*alcohol exposed*) is placed at the end of the name. When alcohol exposure receives a rank of 2, (*alcohol exposure unknown*) is placed at the end of the name.



The 4-Digit Code 3242 would receive the clinical name *sentinel physical findings / static encephalopathy / alcohol exposure unknown.* A code of 1223 would receive the clinical name *neurobehavioral disorder / alcohol exposed.*

Which new Diagnostic Categories represent the category we use to call FAE?

Diagnostic Categories E through I would have previously been referred to as "fetal alcohol effects", "alcohol related birth defects" or "alcohol related neurobehavioral disorder". Categories J through V are new categories that describe a large number of patient groups who have never been adequately classified or described in the past.

How do you explain the diagnosis to the patient?

At the end of this manual (Section VII) are summary explanations for each of the 22 Clinical Diagnostic Categories. These summaries can be used as the first page of the patient's final medical summary note.

III. Diagnostic Evaluation Form Instructions

B.1. Scoring Growth Deficiency

What type of growth deficiency are we looking for?

We are looking for growth deficiency characteristic of a teratogenic insult, not characteristic of postnatal environmental factors such as nutritional deprivation or chronic illness. We want to answer the question '*What is the patient's growth potential after controlling for parental height and postnatal environmental influences?'* Growth deficiency of teratogenic origin is likely to present as a relatively consistent impairment over time (i.e., the patient's growth follows the normal curve, but is below genetic expectation for family background). In contrast, growth deficiency due to postnatal environmental influences is likely to present as periodic fluctuations in the curve. Separating the two growth patterns requires astute clinical judgment.

The method described below allows one to rank a patient's overall growth pattern on a single 4-point Likert scale with 1 equal to normal and 4 equal to significantly deficient. Not all patients will have complete growth curves available, therefore, a guide is provided below for prioritizing the ranking of the patient's growth over a lifetime

Method for ranking the growth component of the 4-Digit Diagnostic Code

A. Height should be age and gender adjusted and should be adjusted for parental height, if possible.

B. Weight should be age and gender adjusted. Weight is not adjusted for height. Normal growth charts are provided in Section VIII.

C. For ranking purposes, the growth curve is separated into two parts:
   1. Prenatal growth (birth measures)
   2. Postnatal growth (all measures collected after birth)

   Select the part of the growth curve with the greatest deficiency in the height centile.

   If the prenatal height centile is lower than all postnatal height centiles, proceed to section D for instructions on how to rank prenatal growth.

   If any of the postnatal height centiles are lower than the prenatal height centile, select the point or consecutive points on the curve that reflect the lowest height centiles that cannot be attributed to postnatal environmental influences such as nutritional deprivation or chronic illness. If the height deficiency is reflected in a series of points on the curve, as opposed to a single point, rank the level of deficiency based on the centile range where the majority of the points fall. Proceed to section D for instructions.

D. Rank the level of deficiency of the height and weight centiles for the section of the curve with greatest deficiency in the height centile by circling A, B or C in the ABC-Score table at the bottom of page 1 of the FAS Diagnostic Evaluation Form. This ABC-Score table is duplicated below as Table 1.

Table 1: Deriving the ABC-Score for Growth

Centile Range	Circle the ABC-Score for: Height	Weight
≤ 3rd	C	C
>3rd and ≤ 10th	B	B
>10th	A	A

E. Next, refer to Table 2 to determine the *4-Digit Diagnostic Code Rank* of the Height-Weight ABC-Score recorded in Table 1. Transfer the resulting 4-Digit Diagnostic Code Rank for growth to the 4-Digit Diagnostic Code Grid at the top of page 1 of the FAS Diagnostic Evaluation Form.

Table 2: Converting the Growth ABC-Score to a 4-Digit Diagnostic Code Rank for Growth

4-Digit Diagnostic Code Rank	Growth Deficiency Category	Height-Weight ABC-Score Combinations
4	Severe	CC
3	Moderate	CB, BC
2	Mild	CA, BB, AC
1	None	BA, AB, AA

Example for Scoring Growth Deficiency

Patient's Growth Record:

	Age (years)	Height Centile	Weight Centile
birth	0.0	5 %	2 %
	1.5	10 %	15 %
	5.0	12 %	20 %
	7.0	12 %	10 %
	15.5	15 %	30 %

Assume the clinical records rule-out any environmental influence on postnatal measures.

Scoring:

- Priority would be placed on ranking the birth measures because the birth height centile is lower than all postnatal height centiles recorded.
- Birth height would be ranked **> 3rd and ≤ 10th** (or Rank B) in Table 1.
  Birth weight would be ranked **≤ 3rd** (or Rank C) in Table 1.

Table 1: Deriving the ABC Score for Growth

	Circle the ABC-Scores for:	
Centile Range	Height	Weight
≤ 3rd	C	**C**
>3rd and ≤ 10th	**B**	B
>10th	A	A

- The Height-Weight ABC-Score would be **BC** according to Table 2.
- The Growth Deficiency Category would be **Moderate** according to Table 2.
- Moderate growth deficiency receives a rank of **3** in the 4-Digit Diagnostic Code in Table 2.

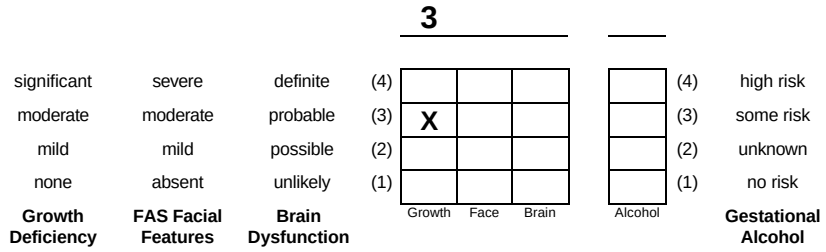
Table 2: Converting the Growth ABC-Score to a 4-Digit Diagnostic Code Rank for Growth

4-Digit Diagnostic Code Rank	Growth Deficiency Category	Height-Weight ABC-Score Combinations
4	Severe	CC
3	**Moderate**	CB, **BC**
2	Mild	CA, BB, AC
1	None	BA, AB, AA

The number **3** would be transferred to the 4-Digit Diagnostic Code Grid on page 1 of the FAS Diagnostic Evaluation Form (as duplicated below).

Result:

4-Digit Diagnostic Code Grid



III. Diagnostic Evaluation Form Instructions

B.2. Scoring the Facial Phenotype

Method for ranking the facial phenotype component of the 4-Digit Diagnostic Code

A. The largest palpebral fissure length (PFL) is measured and ranked according to its z-score (or how many standard deviations above or below the norm it is). The palpebral fissures are adjusted for age and when possible, race. Eyes must be wide open to obtain accurate measures[16, 17]. A normal palpebral fissure length chart is provided in Section VIII[18].

B. The upper lip and philtrum are measured independently using the 5-point pictorial Likert scale presented on the Lip-Philtrum Guide (Figure 1). Lips must be gently closed with no smile to obtain accurate measures (Figure 2)[17]. The physician's eyes must be in the patient's Frankfort Horizontal plane (represented by a line drawn from the external auditory canal to the lower border of the orbital rim). This is crucial for accurate measurement of upper lip thinness (Figure 3)

C. Rank the size, smoothness and thinness of the fissures, philtrum, and upper lip respectively by circling A, B, or C in each column in the ABC-Score table at the bottom of page 2 of the FAS Diagnostic and Evaluation Form. This table is duplicated below as Table 3.

Table 3: Deriving the ABC-Score for Facial Phenotype

5-Point Likert Scale for Philtrum & Lip	Z-score* for Largest Palpebral Fissure	Circle the ABC-Scores for: Palpebral Fissure	Philtrum	Upper Lip
4 or 5	≤ -2 SD	C	C	C
3	>-2 SD and ≤ -1 SD	B	B	B
1 or 2	> -1 SD	A	A	A

* z-score = (patient PFL - normal population PFL)/(normal population PFL standard deviation)

D. Next, refer to Table 4 to determine the *4-Digit Diagnostic Code Rank* based on the ABC-Score derived from Table 3. Transfer the resulting 4-Digit Diagnostic Code Rank for face to the 4-Digit Diagnostic Code Grid on page 1 of the FAS Diagnostic Evaluation Form.

Table 4: Converting the Facial ABC-Score to a 4-Digit Diagnostic Code Rank for Face

4-Digit Diagnostic Code Rank*	Level of Expression of FAS Facial Features	Palpebral Fissure - Philtrum - Lip ABC-Score Combinations
4	Severe	CCC
3	Moderate	CCB, CBC BCC
2	Mild	CCA, CAC, CBB, CBA, CAB, CAA BCB, BCA, BBC, BAC ACC, ACB, ACA, ABC, AAC
1	Absent	BBB, BBA, BAB, BAA ABB, ABA, AAB, AAA

* If facial measures are available at more than one age, score the age when the FAS phenotype is expressed the most. If FAS features are never expressed, score the face between the ages of 3 and 10 years, or at any age if this age range is not available.

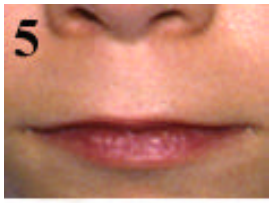
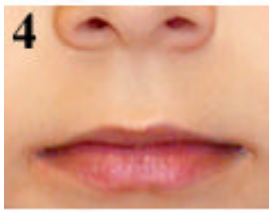
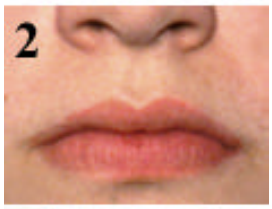
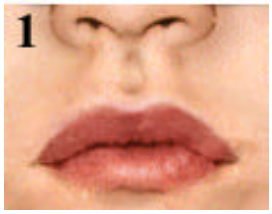
Lip – Philtrum Guide 5-Point Likert Ranks	ABC-Scores Philtrum Smoothness	Upper Lip Thinness	Upper Lip Circularity[12]
	C	C	178
	C	C	80
	B	B	65
	A	A	50
	A	A	35

Figure 1. Pictorial examples of the 5-point Likert scales and the ABC scale used to rank upper lip thinness and philtrum smoothness. It is important that the individual's lips are gently closed with no smile as illustrated in Figure 2.

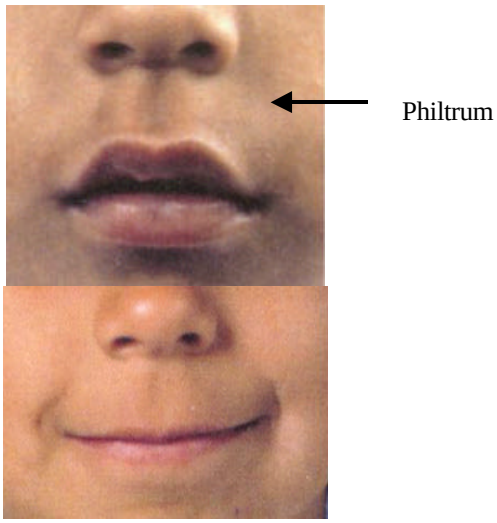


Figure 2. This is the same person with and without a smile. Note that without the smile, the lip and philtrum would both receive a correct Likert rank of # 1. With a smile[19], the lip and philtrum would both receive an incorrect Likert rank of # 5.

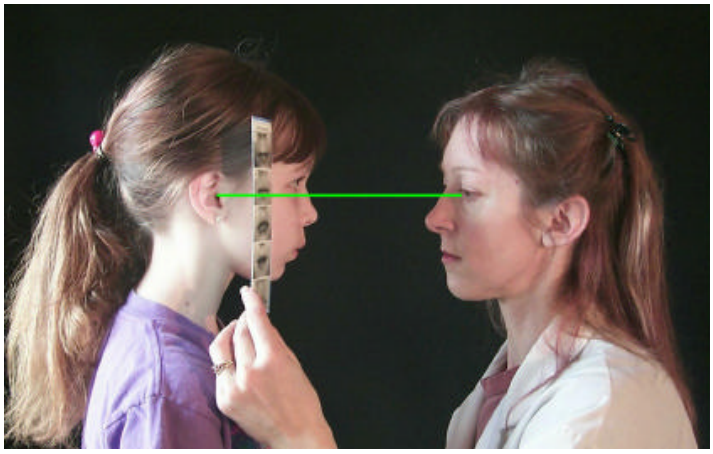


Figure 3. Illustration of a physician aligned in the patient's Frankfort Horizontal plane while using the Lip-Philtrum Guide to rank upper lip thinness and philtrum smoothness. The Frankfort Horizontal plane is defined by a line that passes through the patient's external auditory canal (marked by the tragion) and the lowest border of the bony orbital rim (orbitale). The physician's eyes (or camera lens) should be directly in line with this plane.

Example for Scoring Facial Phenotype

Patient measurements at 10 years of age:

- Palpebral fissure lengths = 2.5 cm which are < -2 SD's from the norm.
- Philtrum smoothness received a score of 5 on the 5-Point photographic Likert scale in Figure 1.
- Upper lip thinness received a score of 3 on the 5-Point photographic Likert scale in Figure 1.

Scoring

- The palpebral fissure lengths receive a Score of “C” in Table 3.

  A philtrum score of 5 corresponds to a score of “C” in Table 3.

  A lip score of 3 corresponds to a score of “B” in Table 3.

- The ABC-Score Combination for Fissure - Philtrum - Lip is **CCB**.

Table 3: Deriving the ABC-Score for Facial Phenotype

5-Point Likert Scale for Philtrum & Lip	Z-score for Largest Palpebral Fissure Length	Circle the ABC-Scores for: Palpebral Fissure	Smooth Philtrum	Thin Upper Lip
4 or 5	≤ -2 SD	**C**	**C**	C
3	>-2 SD and ≤ -1 SD	B	B	**B**
1 or 2	> -1 SD	A	A	A

- A score of CCB indicates that the level of expression of the FAS Facial Features is **MODERATE**.

- A MODERATE expression of the FAS facial features receives a rank of **3** in the 4-Digit Diagnostic Code.

Table 4: Converting the Facial ABC-Score to a 4-Digit Diagnostic Code Rank

4-Digit Diagnostic Code Rank	Level of Expression of FAS Facial Features	Palpebral Fissure - Philtrum - Lip ABC-Score Combinations
4	Severe	CCC
3	**Moderate**	**CCB**, CBC BCC
2	Mild	CCA, CAC, CBB, CBA, CAB, CAA, BCB, BCA, BBC, BAC ACC, ACB, ACA, ABC, AAC
1	Absent	BBB, BBA, BAB, BAA ABB, ABA, AAB, AAA

- Transfer the number **3** to the 4-Digit Diagnostic Code Grid on page 1 of the FAS Diagnostic Evaluation Form (duplicated below).

Result

4-Digit Diagnostic Code Grid

3 ____

				Growth	Face	Brain		Alcohol		
significant	severe	definite	(4)						(4)	high risk
moderate	moderate	probable	(3)		X				(3)	some risk
mild	mild	possible	(2)						(2)	unknown
none	absent	unlikely	(1)						(1)	no risk
Growth Deficiency	**FAS Facial Features**	**Brain Dysfunction**								**Gestational Alcohol**

III. Diagnostic Evaluation Form Instructions

B.3. Scoring Brain Function

Method for ranking the brain function component of the 4-Digit Diagnostic Code

A. Rank Definitions

Brain dysfunction is the most significant disability for individuals damaged by prenatal alcohol exposure. Accurately quantifying and qualifying it is important for both diagnosis and treatment planning. Brain damage can be defined in a large number of ways that are each associated with a broad spectrum of disability. The 4-point Brain Dysfunction Scale (Table 5) allows the clinician to differentiate patients with clear evidence of brain damage (static encephalopathy, Rank 4) from patients without evidence of brain damage (Rank 1). It also introduces two intermediate categories for describing patients who, in the clinician's judgment, cannot be classified as Rank 1 or 4. The higher the number the more *certain* the clinician is that the patient's cognitive and behavioral problems stem from brain damage, but a higher score does not necessarily mean a more severe expression of functional disability. Patients with severe brain dysfunction may not have good evidence for damage at the levels that we can currently study the brain. A patient could simultaneously meet the criteria for both a Rank 3 and 4 on this brain scale. When two scores are both applicable, the higher score is selected for diagnostic purposes because that reflects the level of certainty that there is brain damage.

Brain Rank 4

This rank is selected when the evidence for brain damage is defined through a traditional medical approach. It is our impression that "brain damage" or static encephalopathy is readily diagnosed by clinicians when structural anomalies of the brain are detected or when permanent neurologic findings of presumed prenatal origin are found. Evidence for brain damage includes microcephaly, structural abnormalities of the brain of presumed prenatal origin on a brain image (including, but not limited to hydrocephaly, heterotopias, agenesis of the corpus callosum, etc.), neurologic conditions like seizures which are not due to a postnatal insult or other process, other hard neurologic signs, or a full scale IQ of less than 60.

In this system, at this time, microcephaly is defined as a measurement that is ≤ 2 standard deviations from the mean. Head circumference ≤ 2 standard deviations from the mean has been associated with mental deficiency in the literature[20]. Microcephaly is measured independently of height and weight (i.e. children with height and weight that are less than the second centile and a head circumference of less than the second centile are considered to have the same degree of microcephaly as children who have greater somatic growth).

An IQ of 60 or less was selected for this rank because many experts regard mild mental retardation (IQ of 60-70) as potentially representing the low end of the normal range, while IQ's below 60 seem much more reliably related to true brain abnormality.

Ranking Criteria: One or more positive findings recorded under the Structural or Neurologic headings of the Brain Function section (page 3) of the FAS Diagnostic Evaluation Form are sufficient to classify a patient as Rank 4. A 'positive finding' is defined as a 'Severity of Outcome' score equal to 3.

Brain Rank 3

Through our experience with hundreds of patients who have been exposed to potentially teratogenic doses of ethanol, we have found that many would not qualify as having static encephalopathy using the definition above, but neither could the possibility that they have static encephalopathy be dismissed out of hand. These are typically patients with IQ scores that are above the range clearly indicative of mental retardation, but who often have wide variations in IQ subtest scores, and in addition, have problems with executive functioning, memory and learning, language pragmatics, social adaptation, attention, and/or activity level. These patients have problems that seem likely due to underlying brain structure or function rather than to adverse postnatal environmental experiences.

Ranking Criteria: Three or more significant deficiencies recorded under the Psychometric heading of the Brain Function section (pages 3 and 4) of the FAS Diagnostic Evaluation Form are sufficient to classify a patient as Rank 3. A 'significant deficiency' is defined as a 'Severity of Outcome' score equal to 3.

Brain Rank 2

This score should be given to two groups of patients. All patients in Rank 2 should have histories of behavioral and/or cognitive problems that strongly suggest underlying brain dysfunction. One group of patients has not yet had the types of testing that would move them into Ranks 3 or 4 if positive. The reason for this lack of testing is usually because the patients are too young to be tested (i.e., less than 6 years of age). The other group of patients is those who have had testing that did not reveal compelling evidence for Rank 3 or 4 classification, and yet, in the clinician's judgment, a strong possibility of brain damage can not be wholly dismissed. Alternative testing and/or follow-up testing should usually be considered. If adequately sensitive and appropriate testing has been carried out without clear evidence of brain dysfunction, it is unlikely a Rank 2 classification would be given.

Ranking Criteria: Deficiencies recorded under the Caregiver Interview heading of the Brain Function section (page 5) of the FAS Diagnostic Evaluation Form serve to support a Rank 2 classification. To date, criteria for the number of deficiencies that must be present to warrant a Rank 2 classification have not been established. The classification is made through clinical judgment and the overall weight of evidence obtained.

Brain Rank 1

Patients are classified as Rank 1 when no structural, neurologic or cognitive/behavioral problems measured by psychometric assessment or caregiver interview are discerned.

B. Completing the Brain Function section of the FAS Diagnostic Evaluation Form

The Brain Function section appears on pages 3 through 5 of the FAS Diagnostic Evaluation Form. These pages serve as a place to record pertinent structural, neurologic, pyschometric and caregiver interview data available on the patient. Although space has been provided to record a full complement of assessments, we are not implying that all of these assessments must be conducted to derive a diagnosis. It is the responsibility of the clinical team to select the most appropriate assessment battery. Recording data for the structural, neurologic and psychometric sections is self explanatory. The Caregiver Interview section warrants further explanation.

An important aspect of the FAS evaluation is an in depth interview of the caregivers of the patient. This interview takes approximately one hour and is conducted jointly by the physician and psychologist while the child is being formally assessed by the other clinical staff members. There are several questions that need to be addressed. What are the problems that led to the diagnostic referral? What do the caregivers hope to gain from the assessment? What are the caregivers' views of the patient's overall strengths and weaknesses? What is the child's social and medical history? In addition, we have found it very useful to methodically ask age-appropriate questions that review the patient's functional abilities in domains that are commonly problematic for alcohol exposed individuals according to the literature. These domains (planning, behavioral regulation/sensory motor integration, abstract thinking/judgment, memory/learning/information processing, spatial memory, social skills/adaptive behavior and motor control) are presented on the FAS Diagnostic Evaluation Form (page 5). Routinely asking these questions serves several purposes. First, the caregivers' ability to answer the questions gives insight into their capability of interpreting the patient's behaviors and their general relationship with the patient. Second, it is often helpful to compare this subjective assessment to the psychometric profile to see if discrepancies or deficiencies are present. Third, abnormalities in these domains serve to differentiate Brain Rank 2 from Brain Rank 1. That is, the data needed to establish a Rank 3 or 4 classification is not found, but the reported behaviors of the patient cannot be dismissed as normal variants or transient emotional responses to environmental problems (i.e., depression, post traumatic stress, etc.).

Severity of Outcome Scale [0, 1, 2, 3]

Along the left margin of each page is a Severity of Outcome scale. The clinician is asked to rank the level of abnormality of each outcome as follows: 0 = unable to judge, 1 = normal, 2 = mildly abnormal and 3 = severely abnormal. This ranking process is based on the clinician's clinical judgment and serves to guide him/her in ranking brain dysfunction. For outcomes measured on standardized scales, outcomes ≥ 2 S.D.'s from the norm would be judged severely abnormal.

Table 5: Deriving the 4-Digit Diagnostic Code Rank for Brain Function

4-Digit Diagnostic Code Rank*	Brain Dysfunction Scale	Confirmatory Findings
4	**Definite** *referred to as static encephalopathy*	● Microcephaly, OFC ≤ -2 S. D. *and / or* ● Abnormalities on brain images diagnostic of prenatal alteration *and / or* ● Evidence of persistent neurologic findings likely to be of prenatal origin *and / or* ● I. Q. score ≤ 60
3	**Probable** *referred to as static encephalopathy*	● Substantial deficiencies or discrepancies across multiple areas of brain performance such as cognition, achievement, adaptation, neurologic "soft" signs, and language. Generally three or more areas should be found aberrant.
2	**Possible** *referred to as neurobehavioral disorder*	● Historical information / personal observations strongly suggest the possibility of brain damage, but data to this point does not permit a Rank 3 or 4 classification.
1	**Absent**	● No problems likely to reflect brain damage are presented.

* Transfer the resulting 4-Digit Diagnostic Code Rank for Brain Function to the 4-Digit Diagnostic Code Grid on page 1 of the FAS Diagnostic Evaluation Form.

III. Diagnostic Evaluation Form Instructions

B.4. Scoring Alcohol Exposure

Table 6: Deriving the 4-Digit Diagnostic Code Rank for Alcohol Exposure

4-Digit Diagnostic Code Rank*	Gestational Alcohol Exposure Category	Description
4	High Risk	● Alcohol use during pregnancy CONFIRMED *and* ● Exposure pattern is consistent with the medical literature placing the fetus at "high risk" (generally high peak blood alcohol concentrations delivered at least weekly in early pregnancy).
3	Some Risk	● Alcohol use during pregnancy CONFIRMED *and* ● Drinking occurred in gestation in frequencies and volumes less than in Rank (4) or exact amounts unknown.
2	Unknown Risk	● Gestational exposure is simply not known or information is of questionable reliability
1	No Risk	● Alcohol use during pregnancy is CONFIRMED to be completely ABSENT.

* Transfer the resulting 4-Digit Diagnostic Code Rank for Alcohol Exposure to the 4-Digit Diagnostic Code Grid on page 1 of the FAS Diagnostic Evaluation Form.

III. Diagnostic Evaluation Form Instructions

B.5. Scoring Co-Morbidities

The co-morbidity scales are added for clinical clarification. It is rare that other pre- and/or postnatal factors have not played a role in creating the specific disabilities in a patient with prenatal alcohol exposure. These factors are often helpful in explaining the specific problems faced by the patient and helpful in development of a treatment plan.

A. Prenatal Co-Morbidity Rank Definitions

High Risk (Likert Rank 4):
This Rank is reserved for alternate genetic conditions (e.g., Fragile X, Noonans syndrome, velocardiofacial syndrome, etc.) or teratogenic exposures (e.g., hydantoin, etc.) that have been clearly shown to produce abnormalities.

Some Risk (Likert Rank 3):
This category is used for potential genetic conditions, teratogenic exposures or prenatal conditions that have been associated with physical or neurodevelopmental problems in a less well-established way. Examples of conditions that would be placed in this category would include poor prenatal care; patients whose parents have mild mental retardation, attention deficit, significant learning disabilities or learning problems thought to be due to a non-specific (and non-teratogenic) source; exposure to drugs like marijuana or heroin, in otherwise non-specified frequencies and quantities; and cigarette smoking.

Unknown Risk (Likert Rank 2):
This category is used when the details of the family background and gestation are unknown – generally in the circumstance of a closed adoption.

No Risk (Likert Rank 1):
On occasion, the genetic, teratogenic, and prenatal histories are well documented and no factors can be identified that would explain the abnormalities found in the patient.

B. Postnatal Co-Morbidity Rank Definitions

High Risk (Likert Rank 4):
This Rank is used to note postnatal circumstances that have been shown to have a significant adverse effect on development in most instances. Examples would include physical and sexual abuse, multiple disrupted placements, neglect resulting in failure to thrive, serious head injury, or medical conditions which lead to brain damage (i.e. kernicterus or persistent neonatal apnea).

Some Risk (Likert Rank 3):
This Rank is used to note conditions akin to those in Rank 4, but the circumstances are less severe and so less likely to be a definite factor in the patient's present condition. Obviously, clinical judgment is needed in judging the magnitude of a postnatal problem and interpreting this information into a Rank 3 or 4 placement.

Unknown Risk (Likert Rank 2):
This Rank is used when historical information is missing. This is sometimes the case with adopted children or those in foster care. Adult patients may, at times, be unable to reconstruct their own early histories.

No Risk (Likert Rank 1):
This Rank is used when a well documented history confirms an absence of adverse postnatal events.

IV. Diagnostic Categories

The 256 Diagnostic Codes can be logically grouped into 22 Diagnostic Categories

Category	Name
A	Fetal alcohol syndrome (alcohol exposed)
B	Fetal alcohol syndrome (alcohol exposure unknown)
C	Atypical fetal alcohol syndrome (alcohol exposed)
D	Fetal alcohol syndrome phenocopy (no alcohol exposure)
E	Sentinel physical findings / static encephalopathy (alcohol exposed)
F	Static encephalopathy (alcohol exposed)
G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
H	Neurobehavioral disorder (alcohol exposed)
I	Sentinel physical findings (alcohol exposed)
J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)
K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
L	Static encephalopathy (alcohol exposure unknown)
M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
N	Neurobehavioral disorder (alcohol exposure unknown)
O	Sentinel physical findings (alcohol exposure unknown)
P	No cognitive/behavioral or sentinel physical findings detected (alcohol exposure unknown)
Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
R	Static encephalopathy (no alcohol exposure)
S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
T	Neurobehavioral disorder (no alcohol exposure)
U	Sentinel physical findings (no alcohol exposure)
V	No cognitive/behavioral or sentinel physical findings detected (no alcohol exposure)

V. 4-Digit Diagnostic Codes Within each Diagnostic Category

Category	Diagnostic Name and Codes
A	Fetal alcohol syndrome (alcohol exposed) 3433 4433 3434 4434 3443 4443 3444 4444
B	Fetal alcohol syndrome (alcohol exposure unknown) 3432 4432 3442 4442
C	Atypical fetal alcohol syndrome (alcohol exposed) 1443 1434 2434 3334 4334 4343 2443 1444 2444 3344 4344
D	Fetal alcohol syndrome phenocopy (no alcohol exposure) 3431 4341 4441 3441 4431
E	Sentinel physical findings / static encephalopathy (alcohol exposed) 1333 1433 2344 3143 3243 4133 4233 4333 1334 2333 2433 3144 3244 4134 4234 1343 2334 3133 3233 3333 4143 4243 1344 2343 3134 3234 3343 4144 4244
F	Static encephalopathy (alcohol exposed) 1133 1144 1243 2134 2233 2244 1134 1233 1244 2143 2234 1143 1234 2133 2144 2243
G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed) 1323 2323 3123 3323 4123 4323 1324 2324 3124 3324 4124 4324 1423 2423 3223 3423 4223 4423 1424 2424 3224 3424 4224 4424

Category	Diagnostic Name and Codes
H	Neurobehavioral disorder (alcohol exposed) 1123 2123 1124 2124 1223 2223 1224 2224
I	Sentinel physical findings (alcohol exposed) 1313 2313 3113 3313 4113 4313 1314 2314 3114 3314 4114 4314 1413 2413 3213 3413 4213 4413 1414 2414 3214 3414 4214 4414
J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed) 1113 2113 1114 2114 1213 2213 1214 2214
K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown) 1332 2332 3132 3332 4232 1342 2342 3142 3342 4242 1432 2432 3232 4132 4332 1442 2442 3242 4142 4342
L	Static encephalopathy (alcohol exposure unknown) 1132 1232 2132 2232 1142 1242 2142 2242
M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown) 1322 2322 3122 3322 4122 4322 1422 2422 3222 3422 4222 4422
N	Neurobehavioral disorder (alcohol exposure unknown) 1122 1222 2122 2222
O	Sentinel physical findings (alcohol exposure unknown) 1312 2312 3112 3312 4112 4312 1412 2412 3212 3412 4212 4412

Category	Diagnostic Name and Codes
P	No cogn./behavioral or sentinel physical findings detected (alcohol exposure unknown) 1112 2112 1212 2212
Q	Sentinel physical findings / static encephalopathy (no alcohol exposure) 1331 2341 3231 4141 1341 2431 3241 4231 1431 2441 3331 4241 1441 3131 3341 4331 2331 3141 4131
R	Static encephalopathy (no alcohol exposure) 1131 2131 1141 2141 1231 2231 1241 2241
S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure) 1321 3121 4121 1421 3221 4221 2321 3321 4321 2421 3421 4421
T	Neurobehavioral disorder (no alcohol exposure) 1121 2121 2221 1221
U	Sentinel physical findings (no alcohol exposure) 1311 3111 4111 1411 3211 4211 2311 3311 4311 2411 3411 4411
V	No cognitive/behavioral or sentinel physical findings detected (no alcohol exposure) 1111 2111 1211 2211

VI. 4-Digit Diagnostic Codes Sorted Numerically

Code	Category	Diagnostic Name
1111	V	No cognitive/behavioral or sentinel physical findings detected (no alcohol exposure)
1112	P	No cognitive/behavioral or sentinel physical findings detected (alcohol exposure unknown)
1113	J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)
1114	J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)
1121	T	Neurobehavioral disorder (no alcohol exposure)
1122	N	Neurobehavioral disorder (alcohol exposure unknown)
1123	H	Neurobehavioral disorder (alcohol exposed)
1124	H	Neurobehavioral disorder (alcohol exposed)
1131	R	Static encephalopathy (no alcohol exposure)
1132	L	Static encephalopathy (alcohol exposure unknown)
1133	F	Static encephalopathy (alcohol exposed)
1134	F	Static encephalopathy (alcohol exposed)
1141	R	Static encephalopathy (no alcohol exposure)
1142	L	Static encephalopathy (alcohol exposure unknown)
1143	F	Static encephalopathy (alcohol exposed)
1144	F	Static encephalopathy (alcohol exposed)
1211	V	No cognitive/behavioral or sentinel physical findings detected (no alcohol exposure)
1212	P	No cognitive/behavioral or sentinel physical findings detected (alcohol exposure unknown)
1213	J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)
1214	J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)
1221	T	Neurobehavioral disorder (no alcohol exposure)
1222	N	Neurobehavioral disorder (alcohol exposure unknown)
1223	H	Neurobehavioral disorder (alcohol exposed)
1224	H	Neurobehavioral disorder (alcohol exposed)
1231	R	Static encephalopathy (no alcohol exposure)
1232	L	Static encephalopathy (alcohol exposure unknown)
1233	F	Static encephalopathy (alcohol exposed)
1234	F	Static encephalopathy (alcohol exposed)
1241	R	Static encephalopathy (no alcohol exposure)
1242	L	Static encephalopathy (alcohol exposure unknown)
1243	F	Static encephalopathy (alcohol exposed)
1244	F	Static encephalopathy (alcohol exposed)
1311	U	Sentinel physical findings (no alcohol exposure)
1312	O	Sentinel physical findings (alcohol exposure unknown)
1313	I	Sentinel physical findings (alcohol exposed)
1314	I	Sentinel physical findings (alcohol exposed)
1321	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
1322	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
1323	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)

Code	Category	Diagnostic Name
1324	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
1331	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
1332	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
1333	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
1334	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
1341	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
1342	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
1343	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
1344	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
1411	U	Sentinel physical findings (no alcohol exposure)
1412	O	Sentinel physical findings (alcohol exposure unknown)
1413	I	Sentinel physical findings (alcohol exposed)
1414	I	Sentinel physical findings (alcohol exposed)
1421	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
1422	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
1423	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
1424	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
1431	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
1432	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
1433	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
1434	C	Atypical fetal alcohol syndrome (alcohol exposed)
1441	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
1442	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
1443	C	Atypical fetal alcohol syndrome (alcohol exposed)
1444	C	Atypical fetal alcohol syndrome (alcohol exposed)
2111	V	No cognitive/behavioral or sentinel physical findings detected (no alcohol exposure)
2112	P	No cognitive/behavioral or sentinel physical findings detected (alcohol exposure unknown)
2113	J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)
2114	J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)
2121	T	Neurobehavioral disorder (no alcohol exposure)
2122	N	Neurobehavioral disorder (alcohol exposure unknown)
2123	H	Neurobehavioral disorder (alcohol exposed)
2124	H	Neurobehavioral disorder (alcohol exposed)
2131	R	Static encephalopathy (no alcohol exposure)
2132	L	Static encephalopathy (alcohol exposure unknown)
2133	F	Static encephalopathy (alcohol exposed)
2134	F	Static encephalopathy (alcohol exposed)
2141	R	Static encephalopathy (no alcohol exposure)
2142	L	Static encephalopathy (alcohol exposure unknown)
2143	F	Static encephalopathy (alcohol exposed)
2144	F	Static encephalopathy (alcohol exposed)
2211	V	No cognitive/behavioral or sentinel physical findings detected (no alcohol exposure)
2212	P	No cognitive/behavioral or sentinel physical findings detected (alcohol exposure unknown)
2213	J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)

Code	Category	Diagnostic Name
2214	J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)
2221	T	Neurobehavioral disorder (no alcohol exposure)
2222	N	Neurobehavioral disorder (alcohol exposure unknown)
2223	H	Neurobehavioral disorder (alcohol exposed)
2224	H	Neurobehavioral disorder (alcohol exposed)
2231	R	Static encephalopathy (no alcohol exposure)
2232	L	Static encephalopathy (alcohol exposure unknown)
2233	F	Static encephalopathy (alcohol exposed)
2234	F	Static encephalopathy (alcohol exposed)
2241	R	Static encephalopathy (no alcohol exposure)
2242	L	Static encephalopathy (alcohol exposure unknown)
2243	F	Static encephalopathy (alcohol exposed)
2244	F	Static encephalopathy (alcohol exposed)
2311	U	Sentinel physical findings (no alcohol exposure)
2312	O	Sentinel physical findings (alcohol exposure unknown)
2313	I	Sentinel physical findings (alcohol exposed)
2314	I	Sentinel physical findings (alcohol exposed)
2321	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
2322	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
2323	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
2324	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
2331	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
2332	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
2333	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
2334	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
2341	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
2342	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
2343	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
2344	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
2411	U	Sentinel physical findings (no alcohol exposure)
2412	O	Sentinel physical findings (alcohol exposure unknown)
2413	I	Sentinel physical findings (alcohol exposed)
2414	I	Sentinel physical findings (alcohol exposed)
2421	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
2422	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
2423	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
2424	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
2431	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
2432	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
2433	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
2434	C	Atypical fetal alcohol syndrome (alcohol exposed)
2441	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
2442	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
2443	C	Atypical fetal alcohol syndrome (alcohol exposed)

Code	Category	Diagnostic Name
2444	C	Atypical fetal alcohol syndrome (alcohol exposed)
3111	U	Sentinel physical findings (no alcohol exposure)
3112	O	Sentinel physical findings (alcohol exposure unknown)
3113	I	Sentinel physical findings (alcohol exposed)
3114	I	Sentinel physical findings (alcohol exposed)
3121	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
3122	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
3123	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
3124	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
3131	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
3132	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
3133	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
3134	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
3141	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
3142	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
3143	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
3144	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
3211	U	Sentinel physical findings (no alcohol exposure)
3212	O	Sentinel physical findings (alcohol exposure unknown)
3213	I	Sentinel physical findings (alcohol exposed)
3214	I	Sentinel physical findings (alcohol exposed)
3221	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
3222	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
3223	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
3224	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
3231	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
3232	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
3233	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
3234	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
3241	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
3242	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
3243	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
3244	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
3311	U	Sentinel physical findings (no alcohol exposure)
3312	O	Sentinel physical findings (alcohol exposure unknown)
3313	I	Sentinel physical findings (alcohol exposed)
3314	I	Sentinel physical findings (alcohol exposed)
3321	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
3322	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
3323	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
3324	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
3331	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
3332	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
3333	E	Sentinel physical findings / static encephalopathy (alcohol exposed)

Code	Category	Diagnostic Name
3334	C	Atypical fetal alcohol syndrome (alcohol exposed)
3341	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
3342	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
3343	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
3344	C	Atypical fetal alcohol syndrome (alcohol exposed)
3411	U	Sentinel physical findings (no alcohol exposure)
3412	O	Sentinel physical findings (alcohol exposure unknown)
3413	I	Sentinel physical findings (alcohol exposed)
3414	I	Sentinel physical findings (alcohol exposed)
3421	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
3422	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
3423	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
3424	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
3431	D	Fetal alcohol syndrome phenocopy (no alcohol exposure)
3432	B	Fetal alcohol syndrome (alcohol exposure unknown)
3433	A	Fetal alcohol syndrome (alcohol exposed)
3434	A	Fetal alcohol syndrome (alcohol exposed)
3441	D	Fetal alcohol syndrome phenocopy (no alcohol exposure)
3442	B	Fetal alcohol syndrome (alcohol exposure unknown)
3443	A	Fetal alcohol syndrome (alcohol exposed)
3444	A	Fetal alcohol syndrome (alcohol exposed)
4111	U	Sentinel physical findings (no alcohol exposure)
4112	O	Sentinel physical findings (alcohol exposure unknown)
4113	I	Sentinel physical findings (alcohol exposed)
4114	I	Sentinel physical findings (alcohol exposed)
4121	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
4122	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
4123	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
4124	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
4131	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
4132	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
4133	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
4134	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
4141	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
4142	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
4143	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
4144	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
4211	U	Sentinel physical findings (no alcohol exposure)
4212	O	Sentinel physical findings (alcohol exposure unknown)
4213	I	Sentinel physical findings (alcohol exposed)
4214	I	Sentinel physical findings (alcohol exposed)
4221	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
4222	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
4223	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
4224	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)

Code	Category	Diagnostic Name
4231	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
4232	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
4233	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
4234	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
4241	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
4242	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
4243	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
4244	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
4311	U	Sentinel physical findings (no alcohol exposure)
4312	O	Sentinel physical findings (alcohol exposure unknown)
4313	I	Sentinel physical findings (alcohol exposed)
4314	I	Sentinel physical findings (alcohol exposed)
4321	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
4322	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
4323	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
4324	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
4331	Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
4332	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
4333	E	Sentinel physical findings / static encephalopathy (alcohol exposed)
4334	C	Atypical fetal alcohol syndrome (alcohol exposed)
4341	D	Fetal alcohol syndrome phenocopy (no alcohol exposure)
4342	K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
4343	C	Atypical fetal alcohol syndrome (alcohol exposed)
4344	C	Atypical fetal alcohol syndrome (alcohol exposed)
4411	U	Sentinel physical findings (no alcohol exposure)
4412	O	Sentinel physical findings (alcohol exposure unknown)
4413	I	Sentinel physical findings (alcohol exposed)
4414	I	Sentinel physical findings (alcohol exposed)
4421	S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
4422	M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
4423	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
4424	G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
4431	D	Fetal alcohol syndrome phenocopy (no alcohol exposure)
4432	B	Fetal alcohol syndrome (alcohol exposure unknown)
4433	A	Fetal alcohol syndrome (alcohol exposed)
4434	A	Fetal alcohol syndrome (alcohol exposed)
4441	D	Fetal alcohol syndrome phenocopy (no alcohol exposure)
4442	B	Fetal alcohol syndrome (alcohol exposure unknown)
4443	A	Fetal alcohol syndrome (alcohol exposed)
4444	A	Fetal alcohol syndrome (alcohol exposed)

VII. Clinical Summaries
For each of the 22 Diagnostic Categories

Clinical summaries for each of the 22 Diagnostic Categories are presented on the following pages listed alphabetically from A through V. A complete list of the 22 categories is presented in Section IV.

These summaries can be used as the first page of the final diagnostic report. They often require minor alterations or additions to conform to the specifics of an individual case.

A

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Fetal Alcohol Syndrome**
(2) Alcohol exposed

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of brain damage which occur in individuals exposed to alcohol during gestation. On the attached sheets are the specific findings in this patient's case that led to our conclusion that there was sufficient evidence to make the diagnosis of fetal alcohol syndrome.

Although we believe that the patient clearly has fetal alcohol syndrome, this does not mean that alcohol exposure during pregnancy is the only cause of the patient's current problems. A number of other factors could be contributing to the present situation, such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. Such factors may partly explain why there is so much variability in the kinds of specific difficulties that patients with FAS have.

Individuals with FAS have brain damage as a major component of their cognitive and behavioral problems and should be viewed individuals with disabilities. The fetal alcohol syndrome diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific concerns that have been identified that need attention.

_____ _____

Physician's Signature Date

B

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Fetal Alcohol Syndrome**
(2) Alcohol exposure unknown

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of brain damage occurring in patients exposed to alcohol during gestation. On the attached sheets are the specific findings in this patient's case which led to our conclusion that there was sufficient evidence in this case to make a diagnosis of fetal alcohol syndrome even though the history of exposure to alcohol during gestation could not be confirmed.

Although we believe that the patient clearly has fetal alcohol syndrome, this does not mean that alcohol exposure during pregnancy is the only cause of the patient's current problems. A number of other factors could be contributing to the present issues, such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. Such factors may partly explain why there is so much variability in the kinds of specific difficulties that patients with FAS have.

Individuals with FAS have brain damage as a major component of their cognitive and behavioral problems and should be viewed individuals with disabilities. The fetal alcohol syndrome diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific concerns that have been identified that need attention.

_____ _____
Physician's Signature Date

C

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Atypical Fetal Alcohol Syndrome**
(2) Alcohol exposed

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of brain damage occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS. Indeed, many patients who have been exposed to alcohol show most, but not all, of the classic features of this syndrome. We use the term "atypical fetal alcohol syndrome" when a patient's characteristic features are very close to the classic features of FAS and the alcohol history strongly suggests that alcohol exposure during gestation was at high risk and likely to have played a role in the syndrome. Patients with atypical FAS either have the full set of facial anomalies found with FAS and evidence of brain damage, but do not have growth deficiency; or they have growth deficiency and evidence of brain damage, and most but not all of the FAS facial features. As you can see from the enclosed list of features found in this patient, the patient meets the criteria for atypical FAS. Patients diagnosed with atypical FAS must have confirmed exposure to high levels of alcohol during gestation.

In addition to gestational exposure to alcohol, a number of other factors could be contributing to the patient's current problems, such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. Such factors may partly explain why there is so much variability in the kinds of specific difficulties that patients with FAS experience.

Patients with atypical FAS have brain damage as a major component of their cognitive and behavioral problems and should be viewed as having a disability. The diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific concerns that have been identified that need attention.

_____ _____

Physician's Signature Date

D

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Fetal Alcohol Syndrome Phenocopy**
(2) No alcohol exposure

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of brain damage occurring in patients exposed to alcohol during gestation. On the attached sheets are the specific findings in this patient's case that led to our conclusion that the patient has all of the features of FAS. However, there is good reason to believe this patient was not exposed to alcohol during gestation.

Most syndromes can occasionally arise from an alternate cause. Presumably, this is the situation here. A number of other factors could be contributing to the present situation, such as the patient's genetic background and other potential exposures or problems during pregnancy, and various experiences since birth.

Whatever the cause of this patient's syndrome, there is brain damage which is a major component of their cognitive and behavioral problems and the patient should be viewed as a person with a disability. The syndrome diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific concerns that have been identified that need attention.

_____ _____
Physician's Signature Date

E

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Static encephalopathy**
(2) Sentinel physical findings
(3) Alcohol exposed

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of brain damage in individuals exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, some but not all of the characteristic growth and facial features associated with FAS were present and there was evidence of brain damage as you will see noted on the attached pages. There was also a clear history of exposure to significant amounts of alcohol during gestation. In this situation, we use the terms "static encephalopathy" and "sentinel physical findings" to describe the patient's condition. Static encephalopathy literally means non-progressive brain dysfunction. The diagnoses of "static encephalopathy and sentinel physical findings" in the presence of alcohol exposure do not mean that alcohol is the only cause of the problem. A number of other factors could be contributing to the present issues such as the patient's genetic background, other potential exposures or problems during gestation, and various experiences since birth. These kinds of differences may partly explain why there is so much variability in the kinds of specific difficulties that patients with static encephalopathy and alcohol exposure have.

The diagnoses made today are based on the information available at the time of this assessment. If this patient's alcohol exposure was considered "low risk" and new information is uncovered which documents higher exposures; or if the patient's facial features, growth, or neurobehavioral problems were judged "probable" and further growth or development suggest a "definite" problem is present, then reconsideration of the diagnosis of fetal alcohol syndrome would be appropriate. Alternately other birth defect syndromes not related to alcohol exposure may also need reconsideration.

Individuals with static encephalopathy have brain damage which is a major component of their cognitive and behavioral problems and they should be viewed as individuals with disabilities. The static encephalopathy diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

F

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Static Encephalopathy**
(2) Alcohol exposed

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of brain damage occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, no growth deficiency or characteristic set of facial features were found so the patient does not have FAS, but there was evidence of brain damage as you will see noted on the attached pages. There was also a clear history of exposure to significant amounts of alcohol during gestation. In this situation, we use the term "static encephalopathy" to describe the patient's condition. Static encephalopathy literally means non-progressive brain dysfunction. On the attached sheets are the specific findings in this patient's case that led us to this conclusion. The diagnosis of static encephalopathy does not mean that alcohol is the only cause of the problem. A number of other factors could be contributing to the present issues such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. These kinds of differences may partly explain why there is so much variability in the kinds of specific difficulties that patients with static encephalopathy face.

Individuals with static encephalopathy have brain damage that is a major component of their cognitive and behavioral problems and they should be viewed as individuals with disabilities. The static encephalopathy diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

G

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Neurobehavioral disorder**
(2) Sentinel physical findings
(3) Alcohol exposed

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of brain damage occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS. On the attached sheets you will find our specific observations in this case. We found that some, but not all, of the characteristic physical findings seen in patients with FAS were present. There was not strong evidence that the patient's cognitive/behavioral problems were clearly due to brain damage, but there were suggestions that this was the case. In this situation we use the term "neurobehavioral disorder" to emphasize the possibility that the problems may not be entirely due to postnatal experiences. Certainly a number of other factors could be contributing to the patient's condition such as genetic background, other potential exposures or problems during pregnancy, and various experiences since birth.

The diagnoses made today are based on the information at hand. If further testing is done which makes the likelihood of brain damage of prenatal cause more likely, then an alternate diagnosis could be considered. Alternately other birth defect syndromes not related to alcohol exposure may also need consideration.

In any event, the diagnosis of neurobehavioral disorder means that issues of abnormal brain structure and brain impairment need to be considered with implications for educational planning, societal expectations, and health. On the attached sheet, you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

H

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Neurobehavioral disorder**
(2) Alcohol exposed

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of brain damage in individuals exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

On the attached sheets you will find our specific observations in this case. There was not strong evidence that the patient's cognitive/behavioral problems were clearly due to brain damage, but there were suggestions that this was the case. In this situation we use the term "neurobehavioral disorder" to emphasize the possibility that the problems may not be entirely due to postnatal experiences. Certainly a number of other factors could be contributing to the patient's condition such as genetic background, other potential exposures or problems during gestation, and various experiences since birth.

The diagnosis made today is based on the information available at the time of this assessment. If this patient's alcohol exposure was considered "low risk" and new information is uncovered which documents higher exposure, or if the patient's facial features or growth become more abnormal or if further testing finds further evidence of brain damage, then further diagnostic consideration would be appropriate.

Whatever the cause, the diagnosis of neurobehavioral disorder means that issues of abnormal brain structure and brain impairment need to be considered with implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

I

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Sentinel physical findings**
(2) Alcohol exposed

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of brain damage occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS. Some individuals have the growth deficiency and/or facial characteristics, but do not have evidence of brain damage. We refer to this condition as "Sentinel physical findings / Alcohol exposed". On the attached sheets are the specific findings in this patient's case which indicate that the characteristic growth deficiencies and/or facial features are, to some extent, compatible with FAS, but at this time there is no clear evidence of cognitive or behavioral problems that strongly suggest brain damage. At such time in the future that brain damage is found through images of the brain, neurologic testing or cognitive behavioral assessment, then the diagnosis of fetal alcohol syndrome should be reconsidered. Other birth defect syndromes that are not related to alcohol exposure should also be considered as alternate explanations for the patient's problems.

_____ _____
Physician's Signature Date

J

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis **(1) No cognitive/behavioral or sentinel physical findings detected**
(2) Alcohol exposed

In this current assessment, we conclude that this patient was exposed to alcohol during gestation, but no specific cognitive, behavioral, or characteristic physical findings were detected in our examination.

No alcohol related diagnoses are offered at this time. Re-evaluation would be appropriate in the future if problems arise that strongly suggested brain damage, growth deficiency, or facial dysmorphology.

_____ _____
Physician's Signature Date

K

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis
(1) Static encephalopathy
(2) Sentinel physical findings
(3) Alcohol exposure unknown

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of brain damage in individuals exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, some but not all of the characteristic growth and facial features associated with FAS were present and there was evidence of brain damage as you will see noted on the attached pages. In this situation, we use the terms "static encephalopathy" and "sentinel physical findings" to describe the patient's condition. Static encephalopathy literally means non-progressive brain dysfunction. Although it is unknown whether this patient was exposed to alcohol during gestation, a number of other factors could be contributing to the patient's current cognitive/behavioral problems such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. These kinds of differences may partly explain why there is so much variability in the kinds of specific difficulties that patients with static encephalopathy have.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal, then further diagnostic consideration would be appropriate. Alternately other birth defect syndromes not related to alcohol exposure may also need reconsideration.

Individuals with static encephalopathy have brain damage which is a major component of their cognitive and behavioral problems and they should be viewed as a person with a disability. The static encephalopathy diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

L

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Static encephalopathy**
(2) Alcohol exposure unknown

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of brain damage occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, no growth deficiency or characteristic set of facial features were found so the patient does not have FAS, but there was evidence of brain damage as you will see noted on the attached pages. In this situation, we use the term "static encephalopathy" to describe the patient's condition. Static encephalopathy literally means non-progressive brain dysfunction. On the attached sheets are the specific findings in this patient's case that led us to this conclusion. Although it is unknown whether this patient was exposed to alcohol during gestation, a number of other factors could be contributing to the patient's current cognitive/behavioral problems such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. These kinds of differences may partly explain why there is so much variability in the kinds of specific difficulties that patients with static encephalopathy face.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal, then further diagnostic consideration would be appropriate.

Individuals with static encephalopathy have brain damage that is a major component of their cognitive and behavioral problems and they should be viewed as individuals with disabilities. The static encephalopathy diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

M

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Neurobehavioral disorder**
(2) Sentinel physical findings
(3) Alcohol exposure unknown

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of brain damage occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS. On the attached sheets you will find our specific observations in this case. We found that some, but not all, of the characteristic physical findings seen in patients with FAS were present and a confirmed history of alcohol exposure during gestation was not available. There was not strong evidence that the patient's cognitive/behavioral problems were clearly due to brain damage, but there were suggestions that this was the case. In this situation we use the term "neurobehavioral disorder" to emphasize the possibility that the problems may not be entirely due to postnatal experiences. Certainly a number of other factors could be contributing to the patient's condition such as genetic background, other potential exposures or problems during pregnancy, and various experiences since birth.

The diagnoses made today are based on the information at hand. If further testing is done which makes the likelihood of brain damage of prenatal cause more likely, then an alternate diagnosis would be considered. . Alternately other birth defect syndromes not related to alcohol exposure may also need reconsideration.

In any event, the diagnosis of neurobehavioral disorder means that issues of abnormal brain structure and brain impairment need to be considered with implications for educational planning, societal expectations, and health. On the attached sheet, you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

N

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Neurobehavioral disorder**
(2) Alcohol exposure unknown

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of brain damage in individuals exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

On the attached sheets you will find our specific observations in this case. There was not strong evidence that the patient's cognitive/behavioral problems were clearly due to brain damage, but there were suggestions that this was the case. In this situation we use the term "neurobehavioral disorder" to emphasize the possibility that the problems may not be entirely due to postnatal experiences. Certainly a number of other factors could be contributing to the patient's condition such as genetic background, other potential exposures or problems during gestation, and various experiences since birth.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal or if further testing finds further evidence of brain damage, then further diagnostic consideration would be appropriate.

Whatever the cause, the diagnosis of neurobehavioral disorder means that issues of abnormal brain structure and brain impairment need to be considered with implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

O

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Sentinel physical findings**
(2) Alcohol exposure unknown

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of brain damage occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

Some individuals have the growth deficiency and/or facial characteristics, but do not have evidence of brain damage. We refer to this condition as "Sentinel physical findings". On the attached sheets are the specific findings in this patient's case which indicate that the characteristic growth deficiencies and/or facial features are, to some extent, compatible with FAS, but alcohol exposure during gestation is unknown and at this time there is no clear evidence of cognitive or behavioral problems that strongly suggest brain damage. At such time in the future that brain damage is found through images of the brain, neurologic testing or cognitive behavioral assessment, and a confirmed history of alcohol exposure is obtained, then further diagnostic consideration would be appropriate. Alternately other birth defect syndromes not related to alcohol exposure may also need reconsideration.

_____ _____
Physician's Signature Date

P

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis **(1) No cognitive/behavioral or sentinel physical findings detected**
(2) Alcohol exposure unknown

In this current assessment, it is unknown whether or not this patient was exposed to alcohol during gestation. Furthermore, no specific cognitive, behavioral, or characteristic physical findings were detected in our examination.

No alcohol related diagnoses are offered at this time. Re-evaluation would be appropriate in the future if further history of alcohol use in pregnancy is documented or problems arise that strongly suggested brain damage, growth deficiency, or facial dysmorphology.

_____ _____
Physician's Signature Date

Q

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis
(1) Static encephalopathy
(2) Sentinel physical findings
(3) No alcohol exposure

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of brain damage in individuals exposed to alcohol during gestation.

In this patient's case, some but not all of the characteristic growth and facial features associated with FAS were present, there was evidence of brain damage, and the patient was reportedly not exposed to alcohol during gestation. Based on these observations, which are documented on the attached pages, this patient does not have FAS, but does have static encephalopathy and some of the physical characteristics found after alcohol exposure. Static encephalopathy literally means non-progressive brain dysfunction. A number of factors other than alcohol could be contributing to the patient's current cognitive/behavioral problems such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. The physical findings may suggest that other syndrome diagnoses be considered.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal, then further diagnostic consideration would be appropriate. . Alternately other birth defect syndromes not related to alcohol exposure may also need reconsideration.

Individuals with static encephalopathy have brain damage which is a major component of their cognitive and behavioral problems and they should be viewed as a person with a disability. The static encephalopathy diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

R

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Static encephalopathy**
(2) No alcohol exposure

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of brain damage occurring in patients exposed to alcohol during gestation.

In this patient's case, no growth deficiency or characteristic set of facial features were found and the patient was not exposed to alcohol during gestation so the patient does not have FAS, but there was evidence of brain damage as you will see noted on the attached pages. In this situation, we use the term "static encephalopathy" to describe the patient's condition. Static encephalopathy literally means non-progressive brain dysfunction. On the attached sheets are the specific findings in this patient's case that led us to this conclusion. A number of factors could be contributing to the patient's current cognitive/behavioral problems such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal, then further diagnostic consideration would be appropriate. . Alternately other birth defect syndromes not related to alcohol exposure may also need reconsideration.

Individuals with static encephalopathy have brain damage that is a major component of their cognitive and behavioral problems and they should be viewed as individuals with disabilities. The static encephalopathy diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____

Physician's Signature Date

S

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis
(1) Neurobehavioral disorder
(2) Sentinel physical findings
(3) No alcohol exposure

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of brain damage occurring in patients exposed to alcohol during gestation.

On the attached sheets you will find our specific observations in this case. We found that some, but not all, of the sentinel physical findings seen in patients with FAS were present and the patient was reportedly not exposed to alcohol during gestation. There was not strong evidence that the patient's cognitive/behavioral problems were clearly due to brain damage, but there were suggestions that this may be the case. In this situation we use the term "neurobehavioral disorder" to emphasize the possibility that the problems may not be entirely due to postnatal experiences. The patient also had some of the physical characteristics often found with alcohol exposure. In this case, however, there was no alcohol exposure, therefore, these physical findings might suggest that other syndrome diagnoses be considered. Certainly a number of factors could be contributing to the patient's condition such as genetic background, other potential exposures or problems during pregnancy, and various experiences since birth.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal or if further testing finds further evidence of brain damage, then further diagnostic consideration would be appropriate.

In any event, the diagnosis of neurobehavioral disorder means that issues of abnormal brain structure and brain impairment need to be considered with implications for educational planning, societal expectations, and health. On the attached sheet, you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

T

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Neurobehavioral disorder**
(2) No alcohol exposure

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of brain damage in individuals exposed to alcohol during gestation.

On the attached sheets you will find our specific observations in this case. In this patient's case, no growth deficiency or characteristic set of facial features were found and the patient was not exposed to alcohol during gestation so the patient does not have FAS. Although there was not strong evidence that the patient's cognitive/behavioral problems were clearly due to brain damage, there were suggestions that this may be the case. In this situation we use the term "neurobehavioral disorder" to emphasize the possibility that the problems may not be entirely due to postnatal experiences. Certainly a number of other factors could be contributing to the patient's condition such as genetic background, other potential exposures or problems during gestation, and various experiences since birth.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal or if further testing finds further evidence of brain damage, then further diagnostic consideration would be appropriate. Alternately other birth defect syndromes not related to alcohol exposure may also need reconsideration.

Whatever the cause, the diagnosis of neurobehavioral disorder means that issues of abnormal brain structure and brain impairment need to be considered with implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

U

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Sentinel physical findings**
(2) No alcohol exposure

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies and evidence of brain damage occurring in patients exposed to alcohol during gestation.

On the attached sheets are the specific findings in this patient's case which indicate that characteristic growth deficiencies and/or facial features, compatible with FAS, were present even though the patient was not exposed to alcohol during gestation. In this case, these physical findings might suggest that other syndrome diagnoses be considered.

At such time in the future that brain damage is found through images of the brain, neurologic testing or cognitive behavioral assessment, and/or a confirmed history of alcohol exposure is obtained, then further diagnostic consideration would be appropriate. Alternately other birth defect syndromes not related to alcohol exposure may also need reconsideration.

_____ _____
Physician's Signature Date

V

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis **(1) No cognitive/behavioral or sentinel physical findings detected**
(2) No alcohol exposure

In this current assessment, we conclude that this patient was not exposed to alcohol during gestation. Furthermore, no specific cognitive, behavioral, or characteristic physical findings were detected in our examination.

No diagnoses are offered at this time. Re-evaluation would be appropriate in the future if further history of alcohol use in pregnancy is documented or problems arise that strongly suggested brain damage, growth deficiency, or facial dysmorphology.

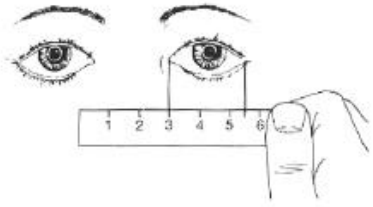
_____ _____
Physician's Signature Date

VIII. Reference Charts of Normal Growth

The attached charts should be used to record standardized measures of palpebral fissure length, inner canthal distance, head circumference, height, weight, and parental height adjustment on the FAS Diagnostic Evaluation Form.

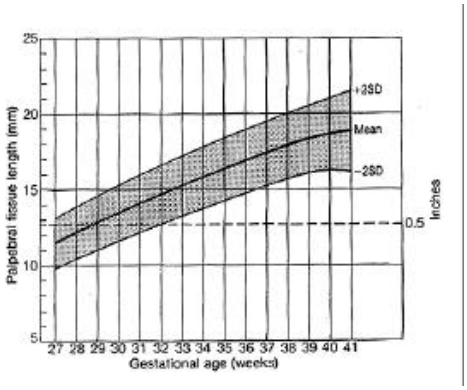
Palpebral Fissure Distance

(From Hall et. al., 1989, by permission)[18]

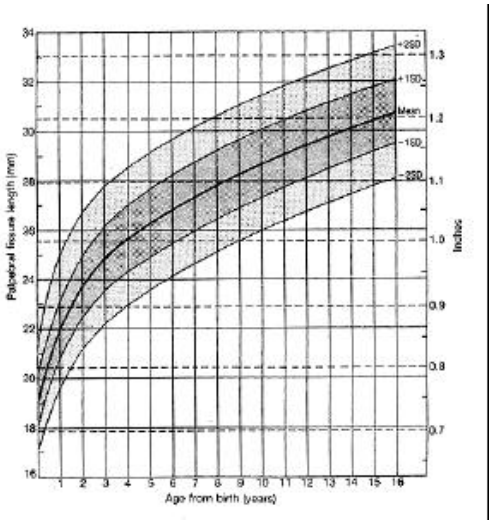


Measure from the inner to the outer canthi.

Have patient look up while holding head level to standardize and maximize fissure length.



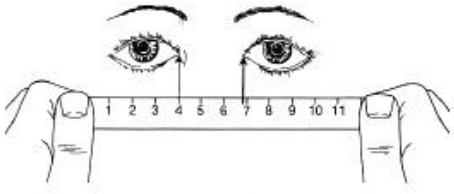
Palpebral fissure length, both sexes, at birth.



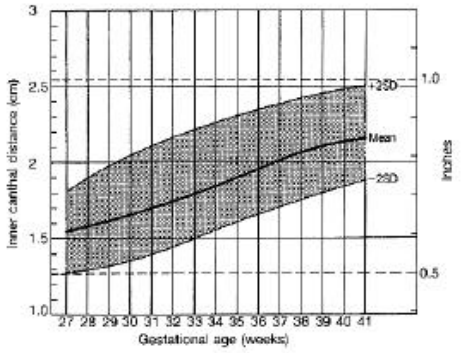
Palpebral fissure length, both sexes, birth to 16 years.

Inner Canthal Distance

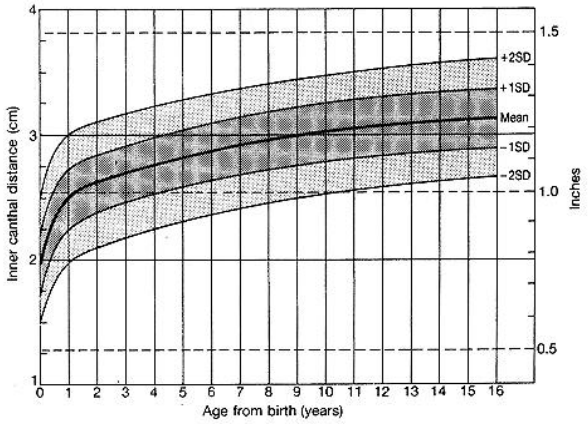
(From Hall et. al., 1989, by permission) [18]



Measure from the innermost corner of each eye, in a straight line avoiding the curvature of the nose.



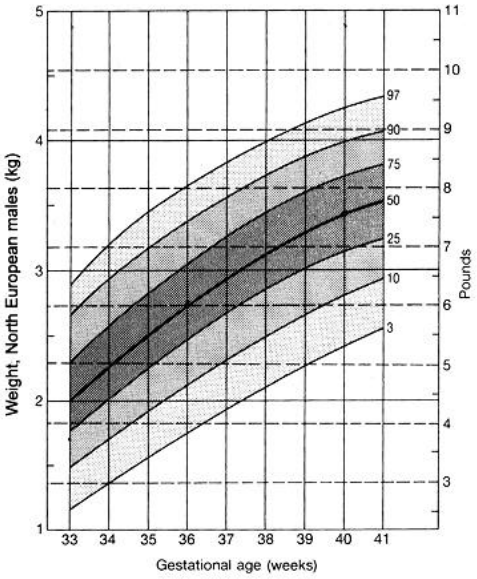
Inner canthal distance, both sexes, at birth.



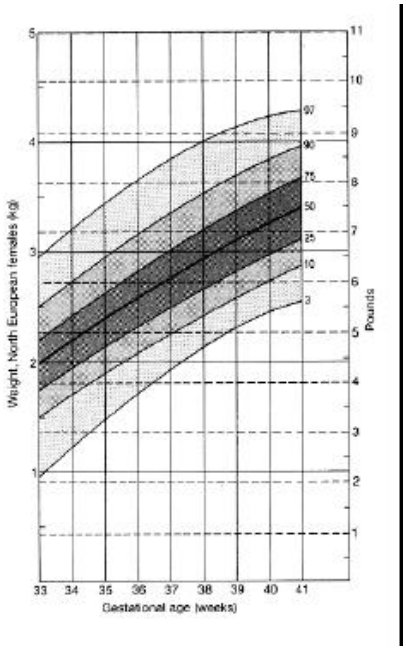
Inner canthal distance, both sexes, birth to 16 years.

Birth Weight

(Hall et. al., 1989, by permission) [18]



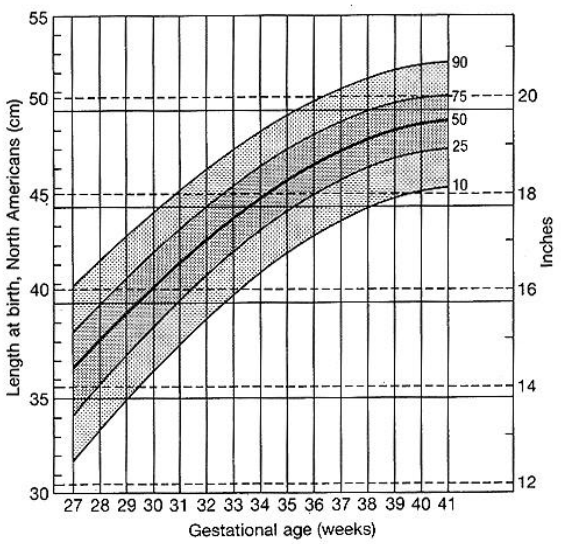
North European males at birth



North European females at birth

Birth Length

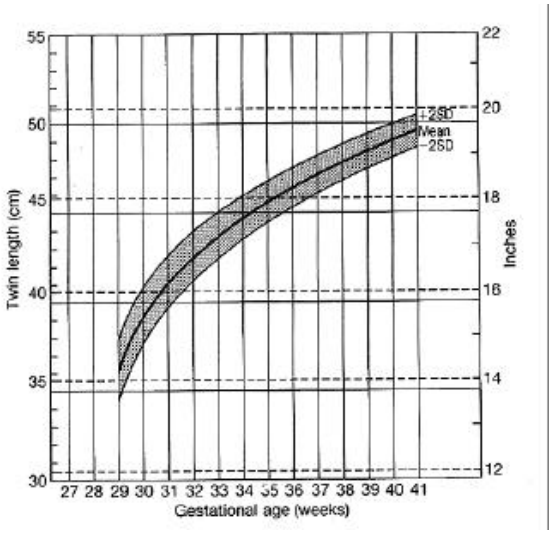
(Hall et. al., 1989, by permission) [18]



Length at birth, North Americans, both sexes.

Birth Length, Twin

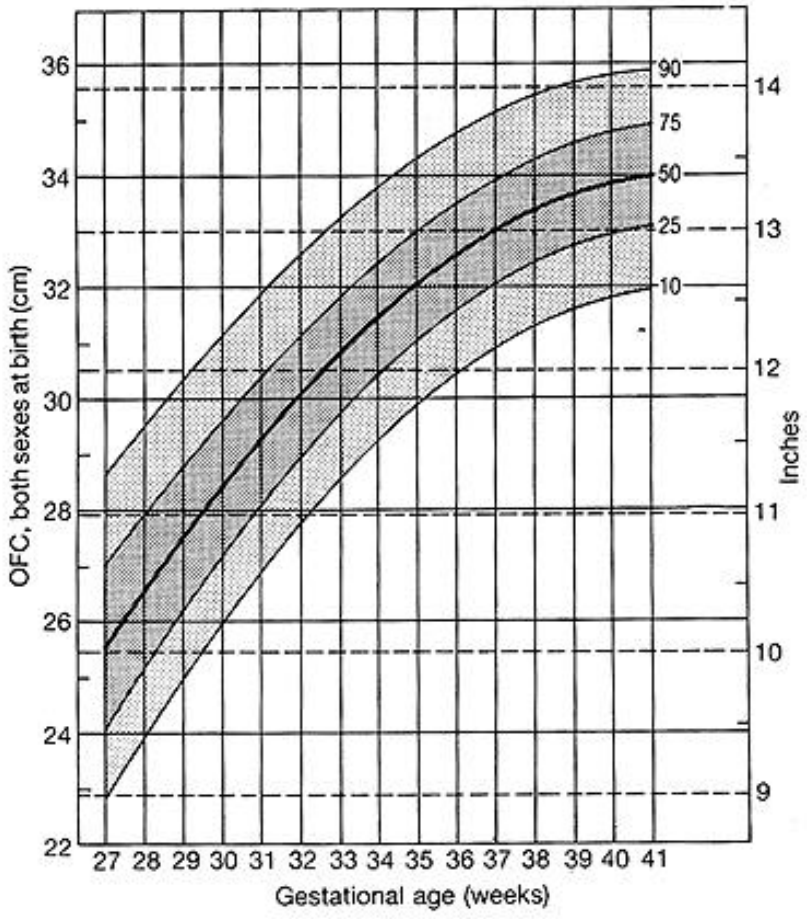
(Hall et. al., 1989, by permission) [18]



Twin length at birth, both sexes.

Head Circumference

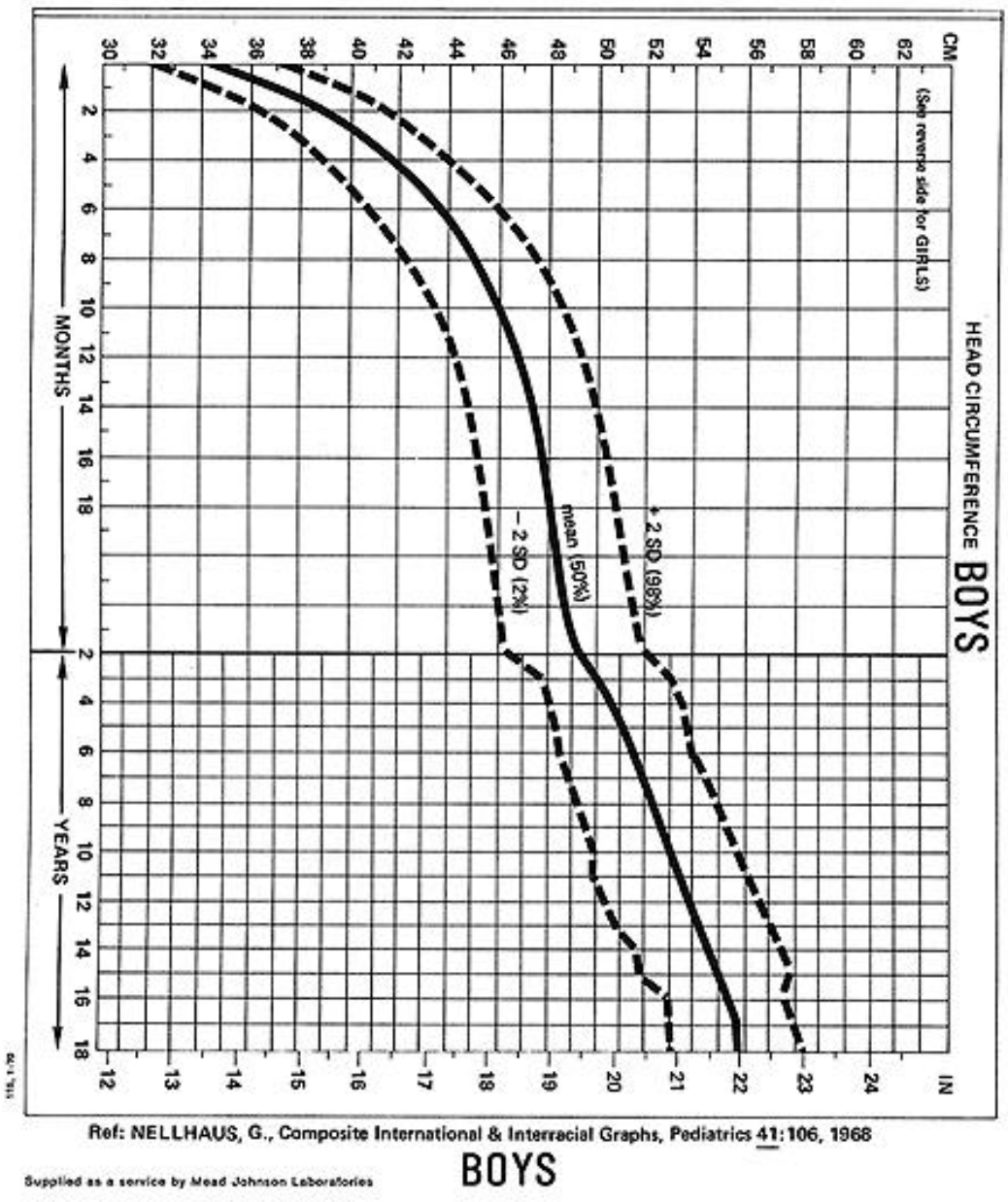
(Hall et. al., 1989, by permission) [18]



Head circumference, both sexes, at birth.

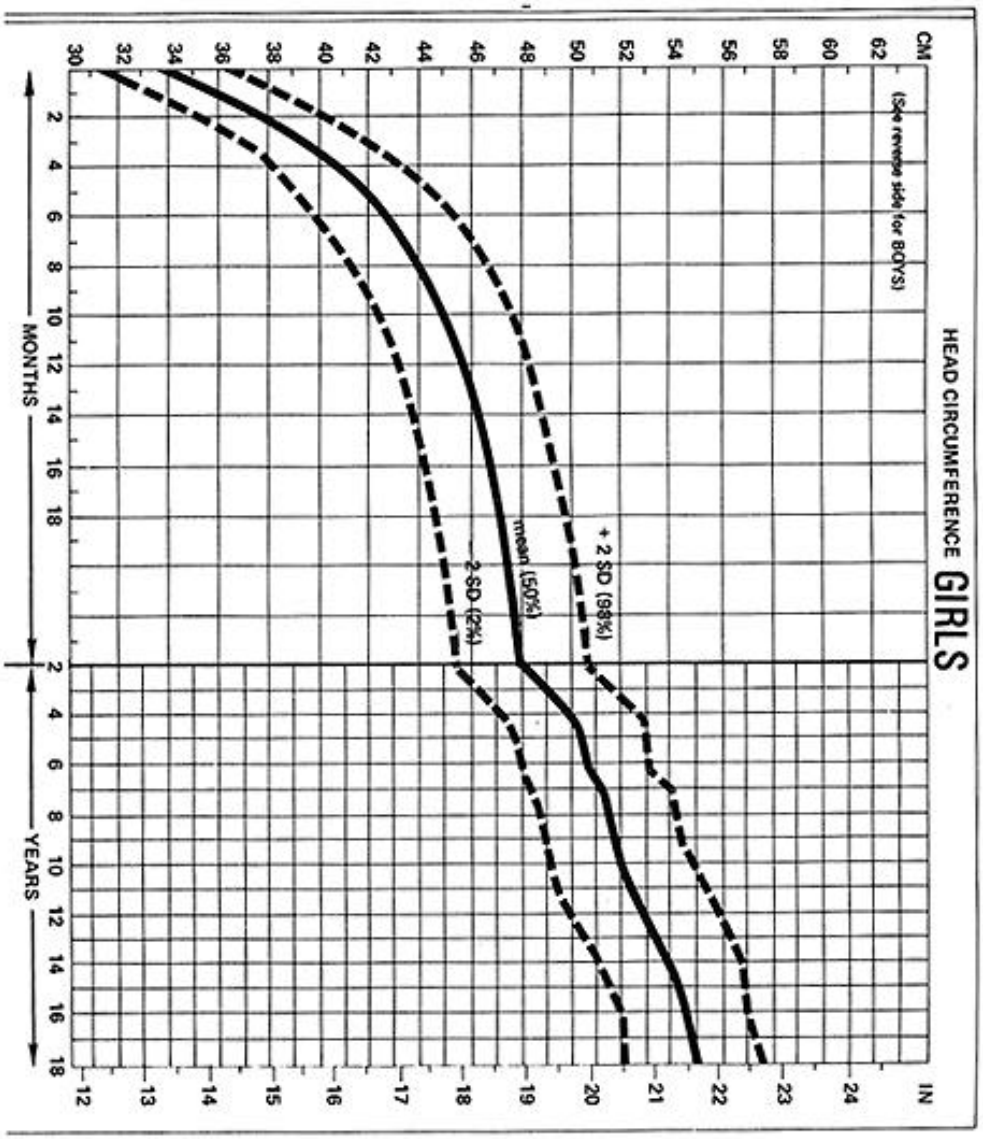
Head Circumference BOYS

(Mead Johnson Nutritionals by permission)[21]



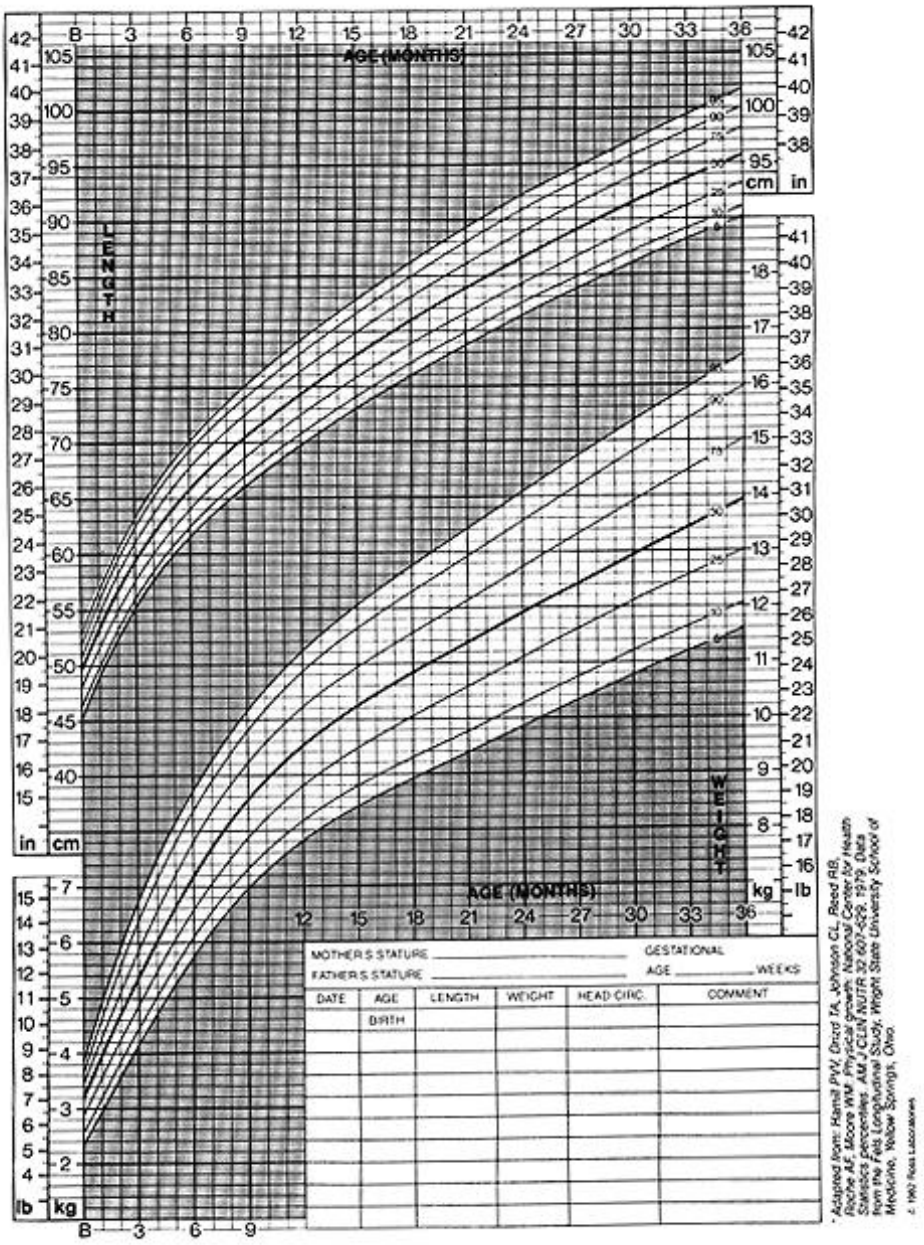
Head Circumference GIRLS

(Mead Johnson Nutritionals by permission)[21]



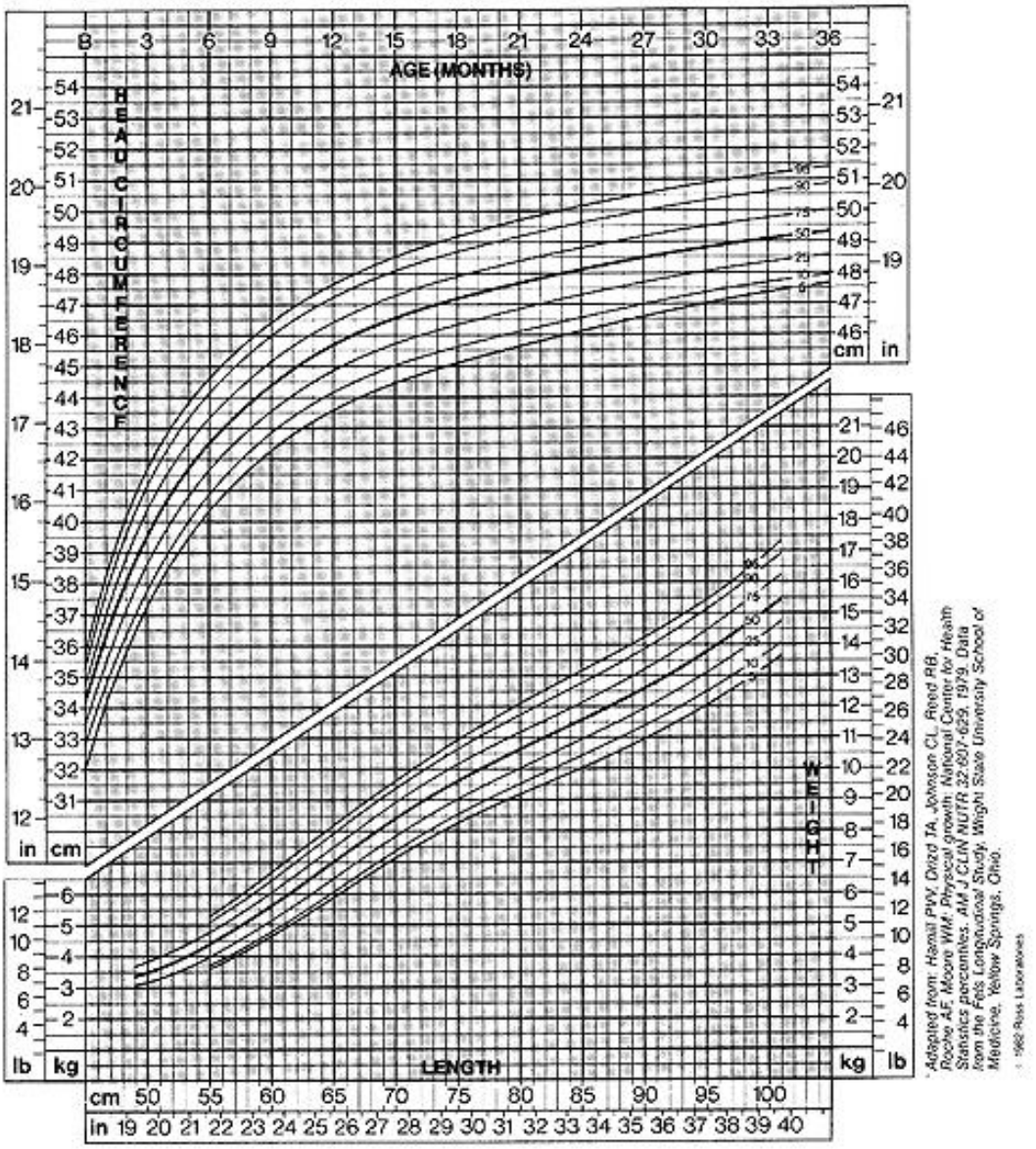
Girls: Birth to 36 Months, Height and Weight, NCHS Percentiles

(Ross Products Division by permission)[22]



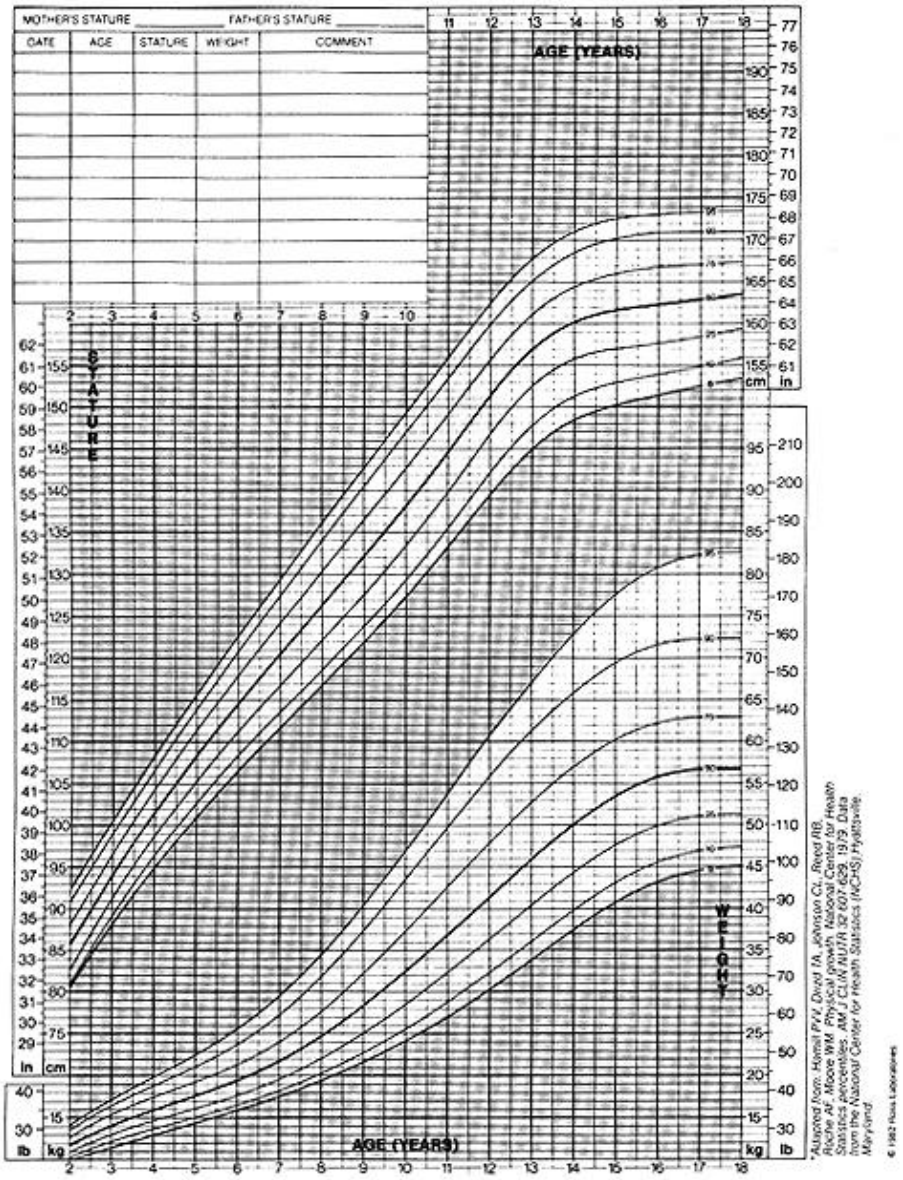
Girls: Birth to 36 Months, Head Circumference, NCHS Percentiles

(Ross Products Division by permission)[22]



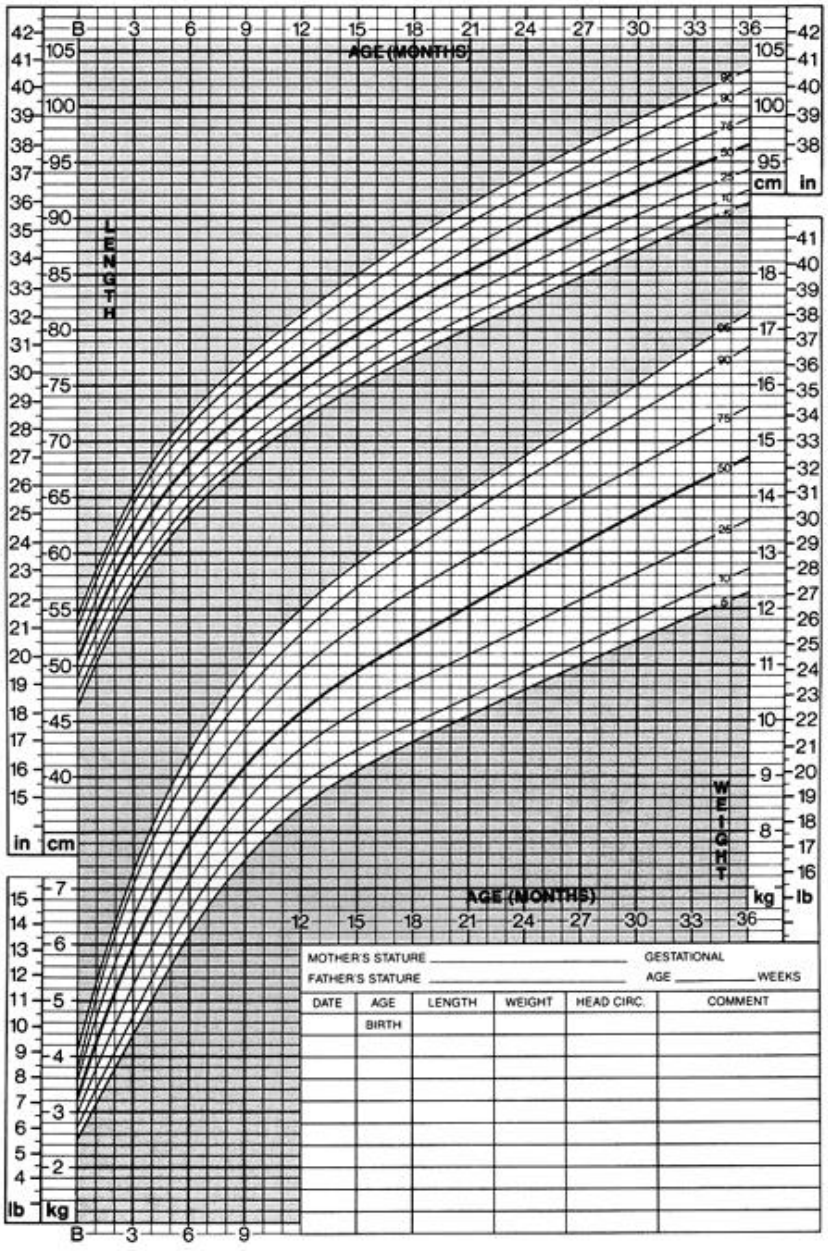
Girls: 2 to 18 Years, Height and Weight, NCHS Percentiles

(Ross Products Division by permission)[23]



Boys: Birth to 36 Months, Height and Weight, NCHS Percentiles

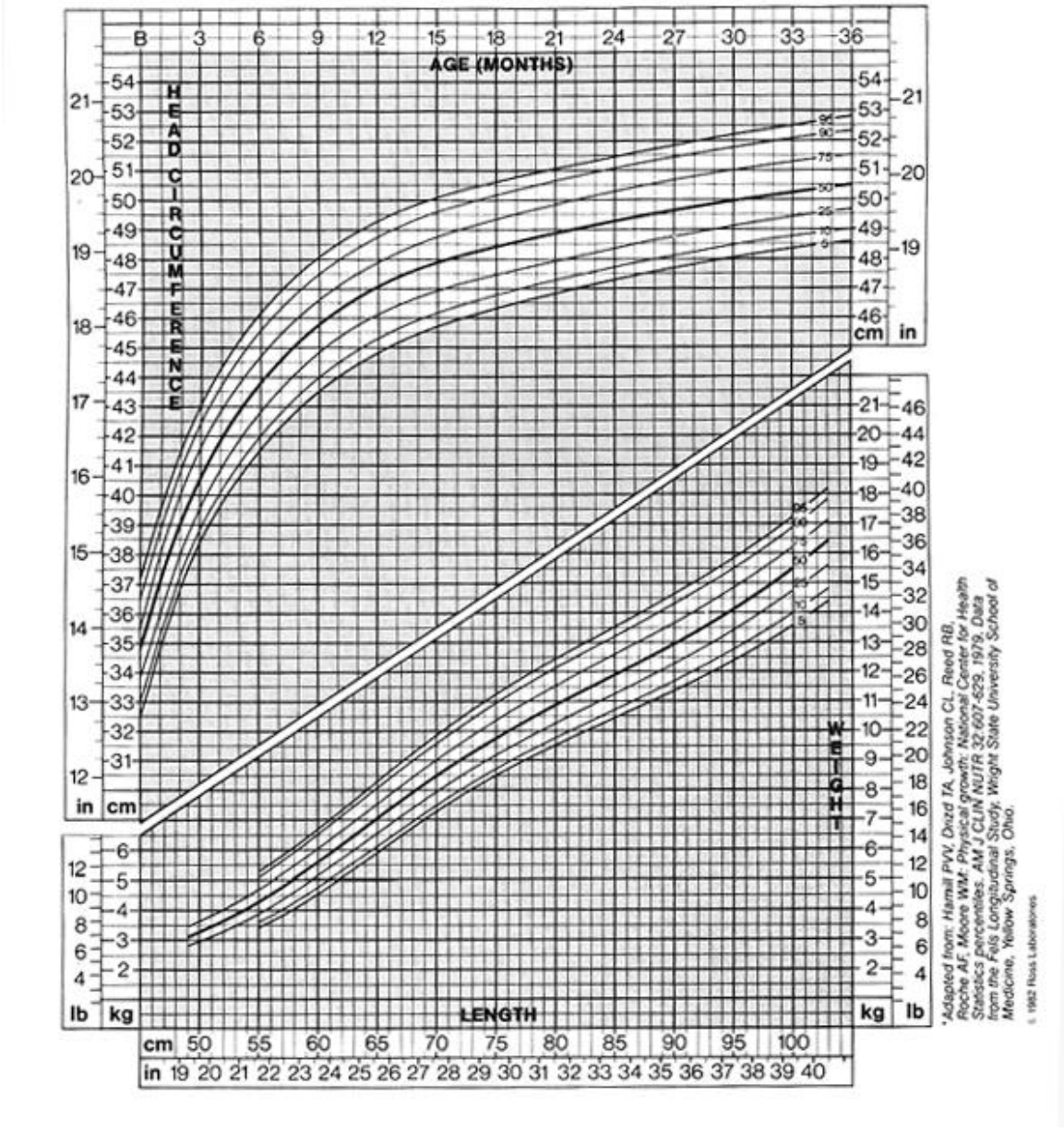
(Ross Products Division by permission)[23]



*Adapted from: Hamill PVV, Drizd TA, Johnson CL, Reed RB, Roche AF, Moore WM: Physical growth: National Center for Health Statistics percentiles. AM J CLIN NUTR 32:607-629, 1979. Data from the Fels Longitudinal Study, Wright State University School of Medicine, Yellow Springs, Ohio.

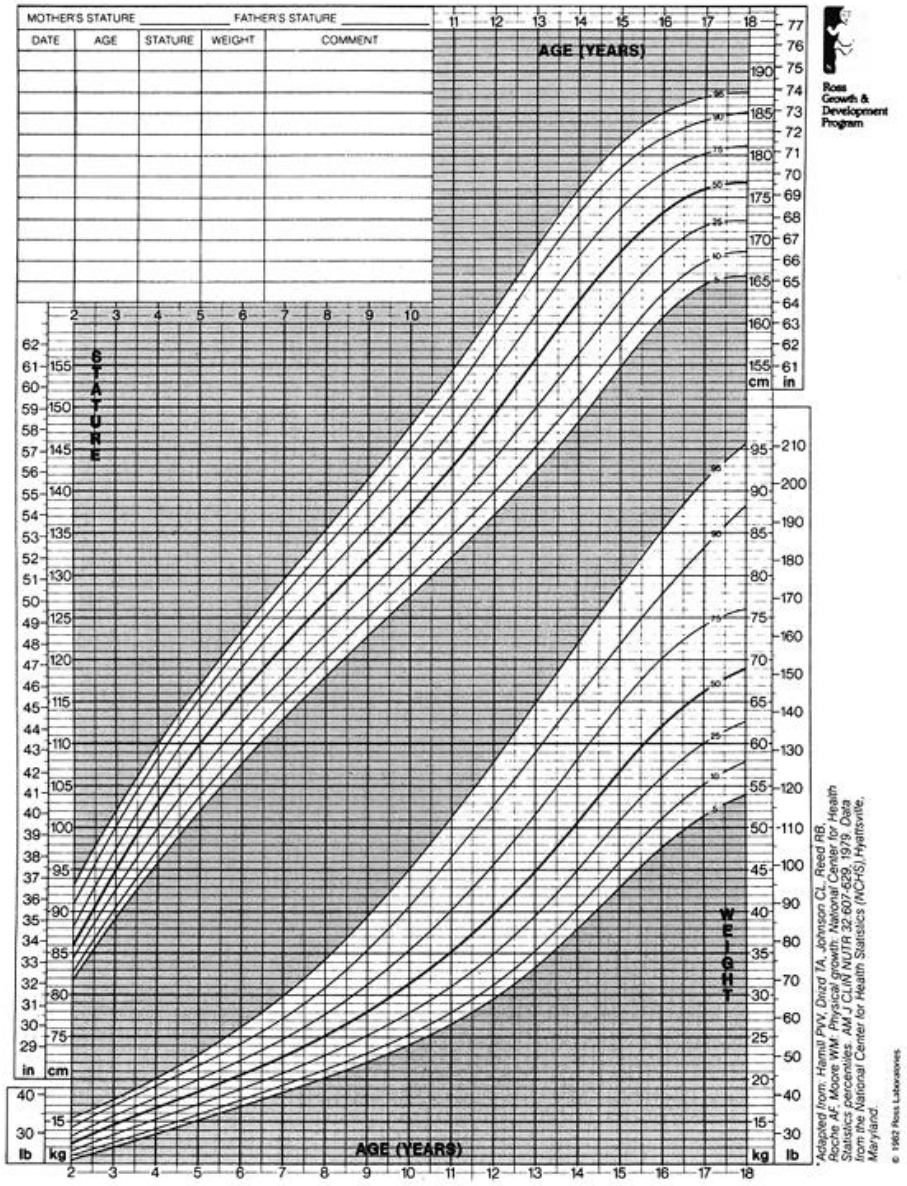
Boys: Birth to 36 Months, Head Circumference, NCHS Percentiles

(Ross Products Division by permission) [22]



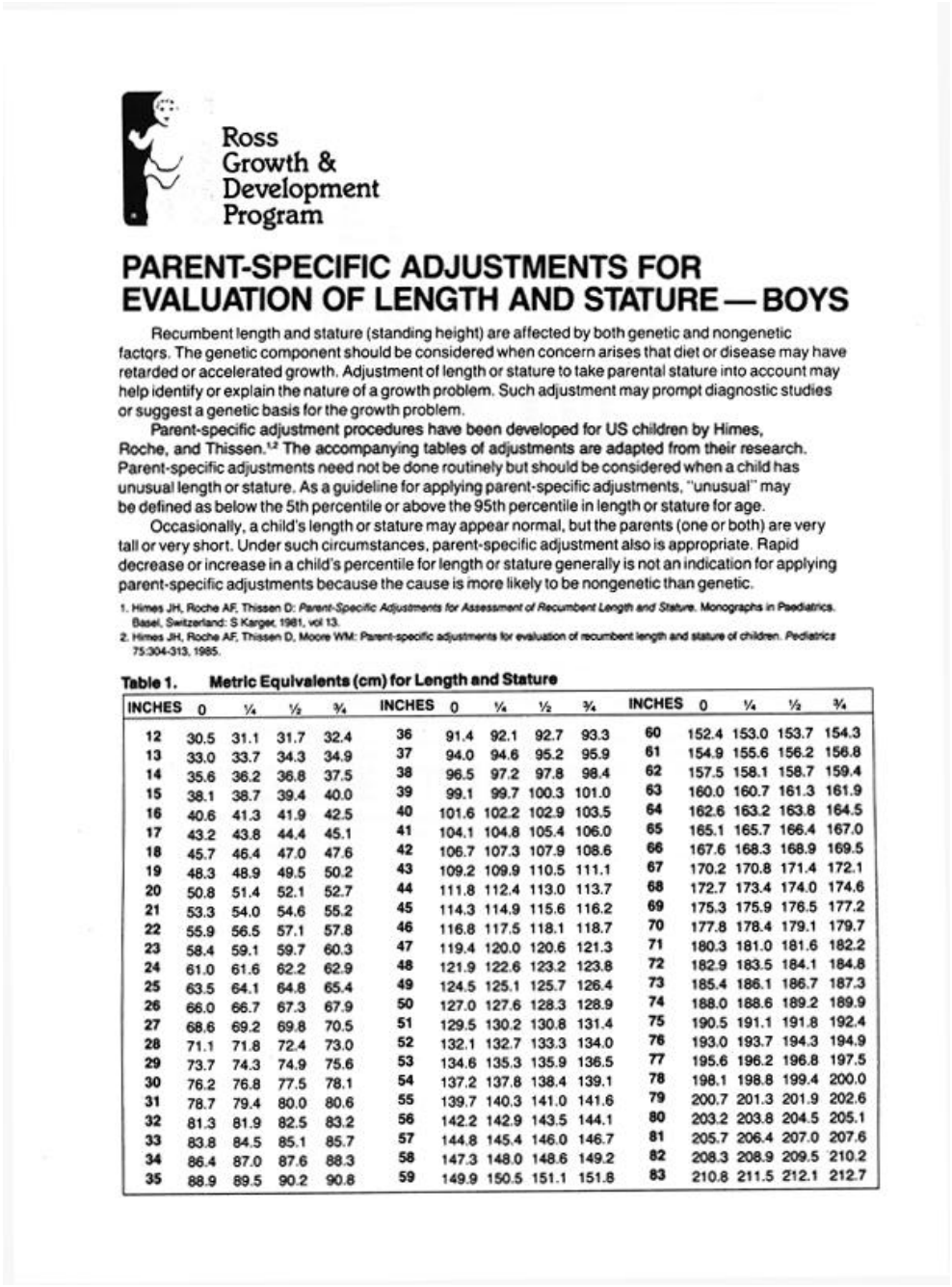
Boys: 2 to 18 Years, Height and Weight, NCHS Percentiles

(Ross Products Division by permission)[23]



Parent Specific Adjustments for Evaluation of Length and Stature

(Ross Laboratories by permission)[24]



Ross
Growth &
Development
Program

PARENT-SPECIFIC ADJUSTMENTS FOR EVALUATION OF LENGTH AND STATURE — BOYS

Recumbent length and stature (standing height) are affected by both genetic and nongenetic factors. The genetic component should be considered when concern arises that diet or disease may have retarded or accelerated growth. Adjustment of length or stature to take parental stature into account may help identify or explain the nature of a growth problem. Such adjustment may prompt diagnostic studies or suggest a genetic basis for the growth problem.

Parent-specific adjustment procedures have been developed for US children by Himes, Roche, and Thissen.[1,2] The accompanying tables of adjustments are adapted from their research. Parent-specific adjustments need not be done routinely but should be considered when a child has unusual length or stature. As a guideline for applying parent-specific adjustments, "unusual" may be defined as below the 5th percentile or above the 95th percentile in length or stature for age.

Occasionally, a child's length or stature may appear normal, but the parents (one or both) are very tall or very short. Under such circumstances, parent-specific adjustment also is appropriate. Rapid decrease or increase in a child's percentile for length or stature generally is not an indication for applying parent-specific adjustments because the cause is more likely to be nongenetic than genetic.

1. Himes JH, Roche AF, Thissen D: *Parent-Specific Adjustments for Assessment of Recumbent Length and Stature*. Monographs in Paediatrics. Basel, Switzerland: S Karger, 1981, vol 13.
2. Himes JH, Roche AF, Thissen D, Moore WM: Parent-specific adjustments for evaluation of recumbent length and stature of children. *Pediatrics* 75:304-313, 1985.

Table 1. Metric Equivalents (cm) for Length and Stature

INCHES	0	¼	½	¾	INCHES	0	¼	½	¾	INCHES	0	¼	½	¾
12	30.5	31.1	31.7	32.4	36	91.4	92.1	92.7	93.3	60	152.4	153.0	153.7	154.3
13	33.0	33.7	34.3	34.9	37	94.0	94.6	95.2	95.9	61	154.9	155.6	156.2	156.8
14	35.6	36.2	36.8	37.5	38	96.5	97.2	97.8	98.4	62	157.5	158.1	158.7	159.4
15	38.1	38.7	39.4	40.0	39	99.1	99.7	100.3	101.0	63	160.0	160.7	161.3	161.9
16	40.6	41.3	41.9	42.5	40	101.6	102.2	102.9	103.5	64	162.6	163.2	163.8	164.5
17	43.2	43.8	44.4	45.1	41	104.1	104.8	105.4	106.0	65	165.1	165.7	166.4	167.0
18	45.7	46.4	47.0	47.6	42	106.7	107.3	107.9	108.6	66	167.6	168.3	168.9	169.5
19	48.3	48.9	49.5	50.2	43	109.2	109.9	110.5	111.1	67	170.2	170.8	171.4	172.1
20	50.8	51.4	52.1	52.7	44	111.8	112.4	113.0	113.7	68	172.7	173.4	174.0	174.6
21	53.3	54.0	54.6	55.2	45	114.3	114.9	115.6	116.2	69	175.3	175.9	176.5	177.2
22	55.9	56.5	57.1	57.8	46	116.8	117.5	118.1	118.7	70	177.8	178.4	179.1	179.7
23	58.4	59.1	59.7	60.3	47	119.4	120.0	120.6	121.3	71	180.3	181.0	181.6	182.2
24	61.0	61.6	62.2	62.9	48	121.9	122.6	123.2	123.8	72	182.9	183.5	184.1	184.8
25	63.5	64.1	64.8	65.4	49	124.5	125.1	125.7	126.4	73	185.4	186.1	186.7	187.3
26	66.0	66.7	67.3	67.9	50	127.0	127.6	128.3	128.9	74	188.0	188.6	189.2	189.9
27	68.6	69.2	69.8	70.5	51	129.5	130.2	130.8	131.4	75	190.5	191.1	191.8	192.4
28	71.1	71.8	72.4	73.0	52	132.1	132.7	133.3	134.0	76	193.0	193.7	194.3	194.9
29	73.7	74.3	74.9	75.6	53	134.6	135.3	135.9	136.5	77	195.6	196.2	196.8	197.5
30	76.2	76.8	77.5	78.1	54	137.2	137.8	138.4	139.1	78	198.1	198.8	199.4	200.0
31	78.7	79.4	80.0	80.6	55	139.7	140.3	141.0	141.6	79	200.7	201.3	201.9	202.6
32	81.3	81.9	82.5	83.2	56	142.2	142.9	143.5	144.1	80	203.2	203.8	204.5	205.1
33	83.8	84.5	85.1	85.7	57	144.8	145.4	146.0	146.7	81	205.7	206.4	207.0	207.6
34	86.4	87.0	87.6	88.3	58	147.3	148.0	148.6	149.2	82	208.3	208.9	209.5	210.2
35	88.9	89.5	90.2	90.8	59	149.9	150.5	151.1	151.8	83	210.8	211.5	212.1	212.7

Parent Specific Adjustments for Evaluation of Length and Stature (continued)

Instructions

INSTRUCTIONS

1. Measure and record mother's stature.
2. Measure and record father's stature.
3. When one parent's stature cannot be measured, the measured parent's estimate of the other parent's stature (in cm) can be substituted for measured stature, and midparent stature can be calculated as in instruction 4. Alternatively, the measured parent's perception of the other parent's stature (short, medium, or tall) can be used to determine midparent stature directly from Table 4.

Table 4. Midparent Stature (cm) When Measured Parent Reports Other Parent's Stature as Short, Medium, or Tall

Measured Parent's Stature (cm)	Midparent Stature (cm)* When Mother Reports Father's Stature as Short†	Medium†	Tall†	When Father Reports Mother's Stature as Short‡	Medium‡	Tall‡
148	156	162	166	150	154	158
148	158	162	166	152	156	160
150	158	164	168	152	156	160
152	160	164	168	154	158	162
154	160	166	170	154	158	162
156	162	168	170	156	160	164
158	162	168	172	156	160	164
160	164	168	172	158	162	166
162	164	170	174	158	162	166
164	166	170	174	160	164	168
166	166	172	176	160	164	168
168	168	172	176	162	166	170
170	168	174	178	162	166	170
172	170	174	178	164	168	172
174	170	176	180	164	168	172
176	172	176	180	166	170	174
178	172	178	182	166	170	174
180	174	178	182	168	172	176
182	174	180	184	168	172	176
184	176	180	184	170	174	178
186	176	182	—	170	174	178
188	178	182	—	172	176	180
190	178	184	—	172	176	180
192	180	184	—	174	178	182
194	180	—	—	174	178	182
196	182	—	—	176	180	184
198	182	—	—	176	180	184

* All midparent statures are rounded to the nearest 2 cm to facilitate use of Tables 2 and 3.
† Values for father's stature used in calculations of midparent stature: short, 167.6 cm (5 ft 6 in.); medium, 176.3 cm (5 ft 9½ in.); tall, 185.4 cm (6 ft 1 in.).
‡ Values for mother's stature used in calculations of midparent stature: short, 154.9 cm (5 ft 1 in.); medium, 162.6 cm (5 ft 4 in.); tall, 170.7 cm (5 ft 7¼ in.).

4. Calculate midparent stature by adding the mother's stature and the father's stature in cm and dividing by two. Metric equivalents for stature are shown in Table 1.
5. Measure, record, and plot the boy's length (birth to 36 months) or stature (3 to 18 years) in cm on the appropriate growth chart that displays the National Center for Health Statistics (NCHS) percentiles. Metric equivalents for length and stature are shown in Table 1.
6. Calculate the boy's adjusted length or stature by using the parent-specific adjustments from Table 2 for length or from Table 3 for stature:
   a. Locate the age closest to that achieved by the boy.
   b. For that age, locate the horizontal row that includes the boy's length or stature.
   c. Locate the vertical column closest to the midparent stature for the boy's mother and father.
   d. The parent-specific adjustment (in cm) appears at the row-column intersection.
   e. Add the parent-specific adjustment to the boy's length or stature if the factor has no sign; subtract the adjustment if it has a minus sign.
7. Determine the boy's parent-specific adjusted percentile by plotting adjusted length or stature on the appropriate NCHS growth chart. Clearly label plotted measurements as being actual or adjusted values.

Interpretation: A boy at a low percentile for actual length or stature whose parents are short probably is genetically short. However, his shortness, particularly if it is extreme, may have additional contributing factors that should be considered.

If the boy's adjusted percentile is low, his growth probably has been slowed by nongenetic factors, and diagnostic studies should be considered. If the parents are tall, the boy's adjusted percentile will be lower than his actual percentile, and his shortness is more likely due to malnutrition or disease.

A boy at a high adjusted percentile for length or stature most often will be found to have accelerated maturation. Rarely, a specific disorder such as Marfan's syndrome or pituitary gigantism may be responsible for the boy's unusual length or stature.

Follow-Up: Counseling may be advisable when a boy is judged to be genetically short or tall. Additional contributing factors should be considered and growth monitored to confirm the relative stability of the boy's length or stature percentile.

Further investigation and modification of diet or specific therapy are indicated for a boy with unusual length or stature due to malnutrition or disease. Growth should be monitored to evaluate the effectiveness of dietary management or drug therapy.

Example #1. Boy aged 12 months, length 28 in., mother's stature 60½ in., and father's stature 65¼ in.

Son's actual length in cm is 71.1 (from Table 1).
Son's actual percentile is below the 5th (from NCHS growth chart).
Mother's stature in cm is 153.7 (from Table 1).
Father's stature in cm is 165.7 (from Table 1).
Midparent stature is $\frac{153.7 + 165.7}{2} = 159.7$ cm.
Adjustment is 2 cm (from Table 2).
Son's adjusted length is 71.1 cm + 2 cm = 73.1 cm.
Son's adjusted percentile is between the 10th and 25th (from NCHS growth chart).
Interpretation: Probably genetically short. Consider additional contributing factors.

Example #2. Boy aged 8 years, stature 47¼ in., mother's stature 68½ in., and father's stature reported as "tall."

Son's actual stature in cm is 120.0 (from Table 1).
Son's actual percentile is 10th (from NCHS growth chart).
Mother's stature in cm is 174.0 (from Table 1).
Midparent stature is 180.0 cm (from Table 4).
Adjustment is − 7 cm (from Table 3).
Son's adjusted stature is 120.0 cm − 7 cm = 113.0 cm.
Son's adjusted percentile is below the 5th (from NCHS growth chart).
Interpretation: Probably nongenetically short. Further investigation is indicated.

Parent Specific Adjustments for Evaluation of Length and Stature

Boys from Birth to 36 Months

Age (Months)	Length (cm)	Midparent Stature (cm)																	
		150	152	154	156	158	160	162	164	166	168	170	172	174	176	178	180	182	184
Birth	40.0– 43.9	2	1	1	1	1	1	1	0	0	0	0	0	0	−1	−1	−1	−1	−1
	44.0– 52.9	2	2	1	1	1	1	1	0	0	0	0	0	0	−1	−1	−1	−1	−1
	53.0– 56.9	2	2	1	1	1	1	1	1	0	0	0	0	0	−1	−1	−1	−1	−1
1	40.0– 44.9	2	2	1	1	1	1	1	0	0	0	0	−1	−1	−1	−1	−1	−2	−2
	45.0– 48.9	2	2	2	1	1	1	1	0	0	0	0	0	−1	−1	−1	−1	−2	−2
	49.0– 52.9	2	2	2	1	1	1	1	1	0	0	0	0	−1	−1	−1	−1	−2	−2
	53.0– 56.9	2	2	2	2	1	1	1	1	0	0	0	0	−1	−1	−1	−1	−1	−2
	57.0– 62.9	2	2	2	2	1	1	1	1	1	0	0	0	0	−1	−1	−1	−1	−2
3	52.0– 56.9	3	2	2	2	1	1	1	1	0	0	0	−1	−1	−1	−1	−2	−2	−2
	57.0– 60.9	3	2	2	2	2	1	1	1	0	0	0	0	−1	−1	−1	−2	−2	−2
	61.0– 66.9	3	3	2	2	2	1	1	1	1	0	0	0	−1	−1	−1	−1	−2	−2
	67.0– 68.9	3	3	2	2	2	2	1	1	1	0	0	0	0	−1	−1	−1	−2	−2
6	62.0– 64.9	3	3	2	2	2	1	1	1	0	0	0	−1	−1	−1	−2	−2	−2	−3
	65.0– 66.9	3	3	3	2	2	2	1	1	1	0	0	−1	−1	−1	−2	−2	−2	−3
	67.0– 73.9	3	3	3	2	2	2	1	1	1	0	0	0	−1	−1	−1	−2	−2	−2
	74.0– 76.9	4	3	3	3	2	2	2	1	1	1	0	0	0	−1	−1	−1	−2	−2
9	66.0– 68.9	3	3	3	2	2	1	1	1	0	0	0	−1	−1	−2	−2	−2	−3	−3
	69.0– 72.9	4	3	3	3	2	2	1	1	1	0	0	−1	−1	−1	−2	−2	−2	−3
	73.0– 76.9	4	3	3	3	2	2	2	1	1	0	0	0	−1	−1	−1	−2	−2	−3
	77.0– 80.9	4	4	3	3	3	2	2	1	1	1	0	0	0	−1	−1	−2	−2	−2
12	67.0– 71.9	4	3	3	2	2	2	1	1	0	0	−1	−1	−1	−2	−2	−3	−3	−3
	72.0– 74.9	4	4	3	3	2	2	1	1	1	0	0	−1	−1	−1	−2	−2	−3	−3
	75.0– 78.9	4	4	3	3	2	2	2	1	1	0	0	0	−1	−1	−2	−2	−3	−3
	79.0– 82.9	4	4	3	3	3	2	2	1	1	1	0	0	−1	−1	−1	−2	−2	−3
	83.0– 84.9	4	4	4	3	3	2	2	2	1	1	0	0	−1	−1	−1	−2	−2	−3
18	73.0– 75.9	4	4	3	3	2	2	1	1	0	0	−1	−1	−2	−2	−2	−3	−3	−4
	76.0– 80.9	4	4	3	3	2	2	2	1	1	0	0	−1	−1	−2	−2	−3	−3	−4
	81.0– 84.9	5	4	4	3	3	2	2	1	1	0	0	−1	−1	−2	−2	−3	−3	−3
	85.0– 88.9	5	4	4	3	3	2	2	1	1	1	0	0	−1	−1	−2	−2	−3	−3
	89.0– 92.9	5	5	4	4	3	3	2	2	1	1	0	0	−1	−1	−2	−2	−2	−3
24	78.0– 82.9	5	4	4	3	3	2	2	1	0	0	−1	−1	−2	−2	−3	−3	−4	−5
	83.0– 86.9	5	5	4	4	3	2	2	1	1	0	0	−1	−2	−2	−3	−3	−4	−4
	87.0– 92.9	6	5	5	4	3	3	2	2	1	1	0	−1	−1	−2	−2	−3	−3	−4
	93.0– 96.9	6	5	5	4	4	3	3	2	1	1	0	0	−1	−1	−2	−3	−3	−4
30	85.0– 88.9	6	5	5	4	3	3	2	1	1	0	−1	−1	−2	−3	−3	−4	−4	−5
	89.0– 92.9	6	5	5	4	4	3	2	2	1	0	0	−1	−2	−2	−3	−3	−4	−5
	93.0– 96.9	6	6	5	4	4	3	3	2	1	1	0	−1	−1	−2	−3	−3	−4	−5
	97.0–100.9	7	6	5	5	4	3	3	2	2	1	0	0	−1	−2	−2	−3	−4	−4
36	88.0– 90.9	6	6	5	4	3	3	2	1	1	0	−1	−1	−2	−3	−4	−4	−5	−6
	91.0– 94.9	6	6	5	4	4	3	2	2	1	0	−1	−1	−2	−3	−3	−4	−5	−5
	95.0– 98.9	7	6	5	5	4	3	3	2	1	1	0	−1	−1	−2	−3	−4	−4	−5
	99.0–102.9	7	6	6	5	4	4	3	2	1	1	0	−1	−1	−2	−3	−3	−4	−5
	103.0–106.9	7	7	6	5	5	4	3	2	2	1	0	0	−1	−2	−2	−3	−4	−4

*Adapted from Himes JH, Roche AF, Thissen D: *Parent-Specific Adjustments for Assessment of Recumbent Length and Stature.* Monographs in Paediatrics. Basel, Switzerland: S Karger, 1981, vol 13, Table XII, pp 36-37.

Parent Specific Adjustments for Evaluation of Length and Stature

Boys from 3 to 18 Years

Age (Years)	Stature (cm)	Midparent Stature (cm)																	
		150	152	154	156	158	160	162	164	166	168	170	172	174	176	178	180	182	184
3	86.0– 87.9	7	6	5	5	4	3	2	1	1	0	−1	−2	−3	−3	−4	−5	−6	−7
	88.0– 97.9	8	7	6	5	4	4	3	2	1	0	−1	−1	−2	−3	−4	−5	−5	−6
	98.0–106.9	8	8	7	6	5	4	4	3	2	1	0	0	−1	−2	−3	−4	−4	−5
4	90.0– 93.9	7	6	5	4	4	3	2	1	0	−1	−1	−2	−3	−4	−5	−5	−6	−7
	94.0–103.9	8	7	6	5	4	3	3	2	1	0	−1	−1	−2	−3	−4	−5	−6	−6
	104.0–112.9	8	8	7	6	5	4	3	3	2	1	0	−1	−1	−2	−3	−4	−5	−6
5	96.0–103.9	8	7	6	5	4	3	2	1	0	0	−1	−2	−3	−4	−5	−6	−7	−8
	104.0–113.9	9	8	7	6	5	4	3	2	1	0	0	−1	−2	−3	−4	−5	−6	−7
	114.0–122.9	9	9	8	7	6	5	4	3	2	1	0	0	−1	−2	−3	−4	−5	−6
6	102.0–111.9	8	7	7	6	5	4	3	2	1	0	−1	−2	−3	−4	−5	−6	−7	−8
	112.0–121.9	9	8	7	7	6	5	4	3	2	1	0	−1	−2	−3	−4	−5	−6	−7
	122.0–130.9	10	9	8	7	6	6	5	4	3	2	1	0	−1	−2	−3	−4	−5	−6
7	108.0–117.9	9	8	7	6	5	4	3	2	1	0	−1	−2	−4	−5	−6	−7	−8	−9
	118.0–127.9	10	9	8	7	6	5	4	3	2	1	0	−1	−2	−4	−5	−6	−7	−8
	128.0–136.9	12	10	9	8	7	6	5	4	3	2	1	0	−1	−2	−4	−5	−6	−7
8	114.0–115.9	10	9	8	6	5	4	3	2	1	−1	−2	−3	−4	−5	−6	−8	−9	−10
	116.0–125.9	11	9	8	7	6	5	4	2	1	0	−1	−2	−3	−5	−6	−7	−8	−9
	126.0–135.9	12	10	9	8	7	6	5	3	2	1	0	−1	−2	−4	−5	−6	−7	−8
	136.0–144.9	13	12	10	9	8	7	6	5	3	2	1	0	−1	−2	−4	−5	−6	−7
9	120.0–121.9	11	9	8	7	6	4	3	2	1	0	−2	−3	−4	−5	−7	−8	−9	−10
	122.0–131.9	11	10	9	8	6	5	4	3	1	0	−1	−2	−3	−5	−6	−7	−8	−10
	132.0–141.9	12	11	10	9	7	6	5	4	2	1	0	−1	−2	−4	−5	−6	−7	−9
	142.0–150.9	13	12	11	10	8	7	6	5	4	2	1	0	−1	−3	−4	−5	−6	−7
10	124.0–127.9	11	10	9	7	6	5	3	2	1	−1	−2	−3	−5	−6	−7	−9	−10	−11
	128.0–137.9	12	11	10	8	7	6	4	3	2	0	−1	−2	−4	−5	−6	−8	−9	−10
	138.0–147.9	13	12	11	9	8	7	5	4	3	1	0	−1	−3	−4	−5	−7	−8	−9
	148.0–158.9	14	13	12	11	9	8	7	5	4	3	1	0	−1	−3	−4	−5	−7	−8
11	128.0–133.9	12	10	9	8	6	5	4	2	1	0	−2	−3	−5	−6	−7	−9	−10	−11
	134.0–143.9	12	11	10	8	7	6	4	3	2	0	−1	−2	−4	−5	−6	−8	−9	−10
	144.0–153.9	14	12	11	10	8	7	5	4	3	1	0	−1	−3	−4	−5	−7	−8	−9
	154.0–162.9	15	13	12	11	9	8	7	5	4	3	1	0	−2	−3	−4	−6	−7	−8
12	132.0–141.9	12	10	9	8	6	5	4	2	1	0	−2	−3	−4	−6	−7	−8	−10	−11
	142.0–151.9	13	11	10	9	7	6	5	3	2	1	−1	−2	−3	−5	−6	−7	−9	−10
	152.0–161.9	13	12	11	9	8	7	5	4	3	1	0	−1	−2	−4	−5	−6	−8	−9
	162.0–170.9	14	13	12	10	9	8	6	5	4	2	1	0	−2	−3	−4	−6	−7	−8
13	136.0–139.9	12	10	9	8	6	5	4	2	1	−1	−2	−3	−5	−6	−7	−9	−10	−12
	140.0–149.9	12	11	10	8	7	6	4	3	1	0	−1	−3	−4	−6	−7	−8	−10	−11
	150.0–159.9	13	12	10	9	8	6	5	4	2	1	−1	−2	−3	−5	−6	−7	−9	−10
	160.0–169.9	14	13	11	10	8	7	6	4	3	2	0	−1	−3	−4	−5	−7	−8	−9
	170.0–178.9	15	13	12	11	9	8	6	5	4	2	1	0	−2	−3	−5	−6	−7	−9
14	142.0–145.9	13	11	10	8	7	5	4	2	1	−1	−2	−4	−5	−7	−8	−10	−11	−13
	146.0–155.9	14	12	11	9	8	6	5	3	1	0	−2	−3	−5	−6	−8	−9	−11	−12
	156.0–165.9	15	13	11	10	8	7	5	4	2	1	−1	−2	−4	−5	−7	−8	−10	−11
	166.0–175.9	15	14	12	11	9	8	6	5	3	2	0	−1	−3	−4	−6	−7	−9	−11
	176.0–184.9	16	15	13	12	10	9	7	6	4	3	1	−1	−2	−4	−5	−7	−8	−10
15	148.0–151.9	14	13	11	9	7	6	4	2	0	−1	−3	−5	−7	−8	−10	−12	−14	−15
	152.0–161.9	15	14	12	10	8	7	5	3	1	0	−2	−4	−6	−7	−9	−11	−13	−14
	162.0–171.9	17	15	13	11	10	8	6	4	3	1	−1	−3	−4	−6	−8	−10	−11	−13
	172.0–181.9	18	16	14	13	11	9	7	6	4	2	0	−1	−3	−5	−7	−8	−10	−12
	182.0–190.9	19	17	16	14	12	10	9	7	5	3	2	0	−2	−4	−5	−7	−9	−11
16	156.0–163.9	17	15	13	11	9	7	5	3	1	−1	−3	−5	−7	−9	−11	−13	−16	−18
	164.0–173.9	19	17	15	13	10	8	6	4	2	0	−2	−4	−6	−8	−10	−12	−14	−16
	174.0–183.9	21	19	17	15	12	10	8	6	4	2	0	−2	−4	−6	−8	−10	−12	−14
	184.0–192.9	23	21	19	17	14	12	10	8	6	4	2	0	−2	−4	−6	−8	−10	−12
17	162.0–165.9	17	15	13	11	9	7	4	2	0	−2	−4	−7	−9	−11	−13	−15	−17	−20
	166.0–175.9	20	17	15	13	11	9	6	4	2	0	−2	−4	−7	−9	−11	−13	−15	−18
	176.0–185.9	22	20	18	16	13	11	9	7	5	3	0	−2	−4	−6	−8	−11	−13	−15
	186.0–194.9	25	23	20	18	16	14	12	9	7	5	3	1	−1	−4	−6	−8	−10	−12
18	160.0–165.9	18	16	13	11	9	6	4	2	0	−3	−5	−7	−10	−12	−14	−17	−19	−21
	166.0–175.9	20	18	16	13	11	9	7	4	2	0	−3	−5	−7	−10	−12	−14	−17	−19
	176.0–185.9	23	21	19	16	14	12	9	7	5	3	0	−2	−4	−7	−9	−11	−14	−16
	186.0–194.9	26	24	22	19	17	15	12	10	8	6	3	1	−1	−4	−6	−8	−11	−13

Parent Specific Adjustments for Evaluation of Length and Stature

Girls from Birth to 36 Months

Age (mo)	Length (cm)	Midparent Stature (cm)																
		150	152	154	156	158	160	162	164	166	168	170	172	174	176	178	180	182	184
Birth	40.0–42.9	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	−1
	43.0–50.9	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	−1
	51.0–54.9	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	46.0–56.9	1	1	1	1	1	1	0	0	0	0	0	0	0	0	−1	−1	−1	−1
	57.0–58.9	1	1	1	1	1	1	1	0	0	0	0	0	0	0	−1	−1	−1	−1
3	52.0–54.9	2	2	1	1	1	1	1	0	0	0	0	0	−1	−1	−1	−1	−2	−2
	55.0–60.9	2	2	2	1	1	1	1	1	0	0	0	0	−1	−1	−1	−1	−1	−2
	61.0–66.9	2	2	2	2	1	1	1	1	0	0	0	0	0	−1	−1	−1	−1	−1
6	58.0–60.9	3	2	2	2	1	1	1	1	0	0	0	−1	−1	−1	−2	−2	−2	−3
	61.0–63.9	3	3	2	2	2	1	1	1	0	0	0	−1	−1	−1	−2	−2	−2	−2
	64.0–68.9	3	3	2	2	2	1	1	1	1	0	0	0	−1	−1	−1	−2	−2	−2
	69.0–72.9	3	3	3	2	2	2	1	1	1	0	0	0	−1	−1	−1	−1	−2	−2
9	64.0–66.9	4	3	3	2	2	2	1	1	0	0	0	−1	−1	−2	−2	−3	−3	−3
	67.0–70.9	4	3	3	3	2	2	1	1	1	0	0	−1	−1	−1	−2	−2	−3	−3
	71.0–73.9	4	4	3	3	2	2	2	1	1	0	0	0	−1	−1	−2	−2	−2	−3
	74.0–76.9	4	4	3	3	3	2	2	1	1	1	0	0	−1	−1	−1	−2	−2	−3
12	66.0–68.9	4	4	3	3	2	2	1	1	0	0	−1	−1	−2	−2	−3	−3	−4	−4
	69.0–72.9	4	4	3	3	2	2	1	1	1	0	0	−1	−1	−2	−2	−3	−3	−4
	73.0–77.9	5	4	4	3	3	2	2	1	1	0	0	−1	−1	−2	−2	−3	−3	−4
	78.0–82.9	5	5	4	4	3	3	2	2	1	1	0	0	−1	−1	−2	−2	−3	−3
18	74.0–76.9	5	4	4	3	2	2	1	1	0	0	−1	−1	−2	−2	−3	−4	−4	−5
	77.0–80.9	5	4	4	3	3	2	2	1	1	0	0	−1	−2	−2	−3	−3	−4	−4
	81.0–84.9	5	5	4	4	3	3	2	2	1	0	0	−1	−1	−2	−2	−3	−3	−4
	85.0–88.9	6	5	5	4	4	3	2	2	1	1	0	0	−1	−1	−2	−2	−3	−4
24	77.0–80.9	5	4	4	3	3	2	1	1	0	0	−1	−2	−2	−3	−3	−4	−5	−5
	81.0–84.9	5	5	4	4	3	2	2	1	1	0	−1	−1	−2	−2	−3	−4	−4	−5
	85.0–88.9	6	5	5	4	3	3	2	2	1	0	0	−1	−1	−2	−3	−3	−4	−4
	89.0–92.9	6	6	5	4	4	3	3	2	1	1	0	0	−1	−2	−2	−3	−3	−4
	93.0–94.9	7	6	5	5	4	4	3	2	2	1	1	0	−1	−1	−2	−2	−3	−4
30	83.0–84.9	6	5	4	4	3	2	2	1	0	0	−1	−2	−2	−3	−4	−4	−5	−6
	85.0–89.9	6	5	5	4	3	3	2	1	1	0	−1	−1	−2	−3	−3	−4	−5	−5
	90.0–94.9	7	6	5	5	4	3	3	2	1	1	0	−1	−1	−2	−3	−3	−4	−5
	95.0–97.9	7	6	6	5	4	4	3	2	2	1	0	0	−1	−2	−2	−3	−4	−4
36	87.0–88.9	6	5	5	4	3	3	2	1	0	0	−1	−2	−2	−3	−4	−5	−5	−6
	89.0–92.9	6	6	5	4	4	3	2	1	1	0	−1	−2	−2	−3	−4	−4	−5	−6
	93.0–96.9	7	6	5	5	4	3	2	2	1	0	0	−1	−2	−3	−3	−4	−5	−5
	97.0–100.9	7	7	6	5	4	4	3	2	1	1	0	−1	−1	−2	−3	−4	−4	−5
	101.0–104.9	8	7	6	6	5	4	4	3	2	1	0	0	−1	−1	−2	−3	−4	−4

[1] Adapted from Himes et al[1] and reprinted with permission from Ross Laboratories, Columbus, OH.

Parent Specific Adjustments for Evaluation of Length and Stature

Girls from 3 to 18 Years

Age (yr)	Stature (cm)	Midparent Stature (cm)																	
		150	152	154	156	158	160	162	164	166	168	170	172	174	176	178	180	182	184
3	82.0–83.9	6	5	4	4	3	2	1	1	0	−1	−1	−2	−3	−3	−4	−5	−6	−6
	84.0–93.9	6	6	5	4	3	3	2	1	1	0	−1	−1	−2	−3	−4	−4	−5	−6
	94.0–102.9	7	7	6	5	4	4	3	2	2	1	0	−1	−1	−2	−3	−3	−4	−5
4	92.0–93.9	6	6	5	4	3	3	2	1	0	0	−1	−2	−3	−3	−4	−5	−6	−7
	94.0–103.9	7	6	6	5	4	3	2	2	1	0	−1	−1	−2	−3	−4	−4	−5	−6
	104.0–112.9	8	7	7	6	5	4	3	3	2	1	0	0	−1	−2	−3	−3	−4	−5
5	100.0–101.9	8	7	6	5	4	3	2	1	1	0	−1	−2	−3	−4	−5	−5	−6	−7
	102.0–111.9	8	7	6	6	5	4	3	2	1	0	−1	−1	−2	−3	−4	−5	−6	−7
	112.0–120.9	9	8	7	7	6	5	4	3	2	1	1	0	−1	−2	−3	−4	−5	−6
6	106.0–109.9	9	8	7	6	5	4	3	2	1	0	−1	−2	−3	−4	−5	−6	−7	−8
	110.0–119.9	9	9	8	7	6	5	4	3	2	1	0	−1	−2	−3	−4	−5	−6	−7
	120.0–128.9	11	10	9	8	7	6	5	4	3	2	1	0	−1	−2	−3	−4	−5	−6
7	112.0–117.9	9	8	7	6	5	4	3	2	1	0	−1	−2	−3	−4	−5	−6	−7	−8
	118.0–127.9	10	9	8	7	6	5	4	3	2	1	0	−1	−2	−3	−4	−5	−6	−7
	128.0–136.9	11	10	9	8	7	6	5	4	3	2	1	0	−1	−2	−3	−4	−5	−6
8	116.0–123.9	9	8	7	6	5	4	3	2	1	0	−1	−2	−3	−4	−5	−6	−8	−9
	124.0–133.9	10	9	8	7	6	5	4	3	2	1	0	−1	−2	−3	−4	−5	−7	−8
	134.0–142.9	11	10	9	8	7	6	5	4	3	2	1	0	−1	−2	−3	−4	−6	−7
9	122.0–131.9	10	9	8	7	6	5	3	2	1	0	−1	−2	−3	−4	−5	−6	−7	−9
	132.0–141.9	11	10	9	8	7	6	4	3	2	1	0	−1	−2	−3	−4	−5	−7	−8
	142.0–150.9	12	11	10	9	8	6	5	4	3	2	1	0	−1	−2	−3	−5	−6	−7
10	126.0–127.9	10	9	7	6	5	4	3	2	1	0	−1	−2	−3	−5	−6	−7	−8	−9
	128.0–137.9	10	9	8	7	6	5	4	2	1	0	−1	−2	−3	−4	−5	−6	−7	−8
	138.0–147.9	11	10	9	8	6	5	4	3	2	1	0	−1	−2	−3	−4	−5	−7	−8
	148.0–156.9	12	10	9	8	7	6	5	4	3	2	1	0	−1	−3	−4	−5	−6	−7
11	130.0–133.9	10	9	8	6	5	4	3	2	1	0	−1	−2	−3	−4	−6	−7	−8	−9
	134.0–143.9	10	9	8	7	6	5	4	3	1	0	−1	−2	−3	−4	−5	−6	−7	−8
	144.0–153.9	11	10	9	7	6	5	4	3	2	1	0	−1	−2	−3	−5	−6	−7	−8
	154.0–162.9	11	10	9	8	7	6	5	4	3	1	0	−1	−2	−3	−4	−5	−6	−7
12	134.0–139.9	10	9	8	7	6	5	3	2	1	0	−1	−3	−4	−5	−6	−7	−8	−10
	140.0–149.9	11	10	9	7	6	5	4	3	2	1	−1	−2	−3	−4	−6	−7	−8	−9
	150.0–159.9	12	10	9	8	7	6	5	3	2	1	0	−1	−3	−4	−5	−6	−7	−8
	160.0–168.9	12	11	10	9	8	6	5	4	3	2	0	−1	−2	−3	−4	−5	−7	−8
13	140.0–145.9	10	9	8	7	6	4	3	2	1	0	−1	−3	−4	−5	−6	−7	−8	−10
	146.0–155.9	11	10	9	7	6	5	4	3	2	0	−1	−2	−3	−4	−6	−7	−8	−9
	156.0–165.9	12	10	9	8	7	6	5	3	2	1	0	−1	−3	−4	−5	−6	−7	−8
	166.0–174.9	12	11	10	9	8	6	5	4	3	2	1	−1	−2	−3	−4	−5	−7	−8
14	146.0–149.9	10	9	8	6	5	4	3	2	1	0	−1	−3	−4	−5	−6	−7	−8	−9
	150.0–159.9	11	9	8	7	6	5	4	3	1	0	−1	−2	−3	−4	−5	−7	−8	−9
	160.0–169.9	11	10	9	8	7	6	5	3	2	1	0	−1	−2	−3	−5	−6	−7	−8
	170.0–178.9	12	11	10	9	8	6	5	4	3	2	1	0	−2	−3	−4	−5	−6	−7
15	146.0–151.9	10	9	8	7	5	4	3	2	1	−1	−2	−3	−4	−5	−6	−8	−9	−10
	152.0–161.9	11	10	9	7	6	5	4	3	1	0	−1	−2	−3	−4	−6	−7	−8	−9
	162.0–171.9	12	11	10	8	7	6	5	4	2	1	0	−1	−2	−4	−5	−6	−7	−8
	172.0–180.9	13	12	11	9	8	7	6	5	3	2	1	0	−1	−3	−4	−5	−6	−7
16	146.0–151.9	11	10	8	7	6	5	3	2	1	−1	−2	−3	−4	−6	−7	−8	−10	−11
	152.0–161.9	12	10	9	8	7	5	4	3	2	0	−1	−2	−4	−5	−6	−7	−9	−10
	162.0–171.9	13	12	10	9	8	6	5	4	3	1	0	−1	−3	−4	−5	−6	−8	−9
	172.0–180.9	14	13	11	10	9	7	6	5	4	2	1	0	−2	−3	−4	−5	−7	−8
17	148.0–153.9	11	10	9	7	6	5	3	2	1	0	−2	−3	−4	−6	−7	−8	−10	−11
	154.0–163.9	12	11	10	8	7	6	4	3	2	0	−1	−2	−4	−5	−6	−8	−9	−10
	164.0–173.9	13	12	11	9	8	7	5	4	3	1	0	−1	−3	−4	−5	−6	−8	−9
	174.0–182.9	14	13	12	10	9	8	6	5	4	2	1	0	−1	3	−4	−5	−7	−8
18	148.0–149.9	10	9	8	7	5	4	3	2	1	−1	−2	−3	−4	−6	−7	−8	−9	−10
	150.0–159.9	11	10	8	7	6	5	4	2	1	0	−1	−3	−4	−5	−6	−7	−9	−10
	160.0–169.9	12	11	9	8	7	6	4	3	2	1	0	−2	−3	−4	−5	−6	−8	−9
	170.0–178.9	13	11	10	9	8	7	5	4	3	2	1	−1	−2	−3	−4	−5	−7	−8

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X. Appendices

A. New Patient Information Form

B. FAS-Tutor™ CD-ROM

New Patient Information Form — FAS Clinic

Office Use: Date received 1 ___/___/___ Deadline ___/___/___ ASAP ___ Response Let. 4 ___/___/___ Photo 5 ___ Screen Code 6 _____
G _____ F _____ B _____ A _____ M _____ : 1 2 3 4

Patient Identification

Patient's Social Security Number *(optional)* 7 _____ 8 ❑ Female ❑ Male Race 9 _____

Patient's Name _____ Birth date 13 _____ Age 14 ____
First 10 *Middle* 11 *Last* 12

Patient's Address _____

City 16 _____ County 17 _____ State 18 _____ zipcode 19 _____

Patient's Telephone Home ( ) _____ Work ( ) _____

Caretaker Identification

Name of patient's primary caretaker(s) _____

Relationship to patient: 23 ❑ birth, ❑ adoptive, or ❑ foster parent ❑ other (specify 24 _____)

Caretaker's Address _____

City _____ County _____ State _____ zipcode _____

Telephone Home ( ) _____ Work ( ) _____

Name of patient's legal guardian(s) _____

Person Completing the Form

Name of person completing this form _____ Date _____

Relationship to patient: 35 ❑ birth, ❑ adoptive, or ❑ foster parent, ❑ caseworker, ❑ medical care provider

❑ other relationship (please specify 36 _____)

Referred by (e.g., who or what organization told you about the clinic ?) 37 _____

Who Should Correspondence be Sent To?

Name _____

Relationship to patient: ❑ birth, ❑ adoptive, or ❑ foster parent ❑ other (specify _____)

Address _____

City _____ County _____ State _____ zipcode _____

Telephone Home ( ) _____ Work ( ) _____

University of Washington FAS Diagnostic & Prevention Network: NPIF8.doc 1/1/99 Patient Name:_____ 1

Please complete this form to the best of your ability. We realize you will not have the answers to all questions. All of the information requested on this form is important in allowing us to provide you with the most accurate diagnosis and most appropriate referrals for care. Thankyou for taking the time to complete it.

Reasons for Evaluation - What are the patient's primary problems? Please be specific.

What do you hope to gain from the evaluation?

Growth

Birth Measures

1. Birth weight: lbs / oz _____ or gms 51 _____

   Birth length: inches _____ or cm 53 _____

   Birth head circumference: inches _____ or cm 55 _____

   Gestational age *(length of pregnancy)*: weeks 56 _____ or months _____

Please provide additional height, weight and head measures if available*

2. Date _____ Weight: lbs _____ or kg _____

   Age _____ Height: inches _____ or cm _____

   Head Circumference: inches _____ or cm _____

3. Date _____ Weight: lbs _____ or kg _____

   Age _____ Height: inches _____ or cm _____

   Head Circumference: inches _____ or cm _____

4. Date _____ Weight: lbs _____ or kg _____

   Age _____ Height: inches _____ or cm _____

   Head Circumference: inches _____ or cm _____

5. Date _____ Weight: lbs _____ or kg _____

   Age _____ Height: inches _____ or cm _____

   Head Circumference: inches _____ or cm _____

Birth Parents' Heights: Birth Mother: inches _____ or cm 91 _____

Birth Father: inches _____ or cm 93 _____

* This information may be available from the patient's physician or school nurse. If growth charts are available and can be photocopied and attached to this form, you need not fill out this section.

University of Washington FAS Diagnostic & Prevention Network: NPIF8.doc 1/1/99 Patient Name:_____ 4

Physical Appearance and Health

1. **Photographs of the patient's face are very helpful to us.** The most helpful show the patient's full face towards the camera in good light without much facial expression (no big smile or frown). Pictures between ages 1 and 12 years are best.

   - Are such photographs available? ____ yes ____ no
   - Are one or two included with this form? ____ yes ____ no
   - Can others be brought to the clinic? ____ yes ____ no

Please staple photo(s) here:

Photo may be bigger than this space

2. **Was the patient born with (or later discovered to have) any birth defects (things like cleft lip, congenital heart defects, club foot, etc.)?** 97 ____ yes ____ no ____ unknown

   If yes, please describe: 98 _____

3. **Has this patient ever had:**

	yes	no	unknown		yes	no	unknown
Allergies	99 ____	____	____	Chronic illness of the heart	104 ____	____	____
Multiple ear infections	100 ____	____	____	Chronic illness of the kidneys	105 ____	____	____
Chronic sinusitis	101 ____	____	____	Chronic illness of the joints/limbs	106 ____	____	____
Chronic hearing loss	102 ____	____	____	Chronic illness of the stomach/ bowels	107 ____	____	____
Visual problems (wears glasses)	103 ____	____	____				

4. **Has this patient ever had:**

   A. **Operations (since birth)** 108 ____ yes ____ no ____ unknown

Describe Operation	Surgeon's Name	Patient's Age

   B. **Any other hospitalizations** 115 ____ yes ____ no ____ unknown

Reason for Hospitalization	Hospital/Doctor	Patient's Age

   C. **Physical abuse** 122 ____ yes ____ no ____ unknown Age(s): 123 _____

   Was this evaluated by a physician? ____ yes ____ no ____ unknown

   D. **Sexual abuse** 125 ____ yes ____ no ____ unknown Age(s): 126 _____

   Was this evaluated by a physician? ____ yes ____ no ____ unknown

Neurologic Issues

1. **Has this patient ever had:**
   A. **Seizures**

128 ____ yes ____ no ____ unknown

Type: 129 _____

Age when seizure(s) started: 130 _____

Name(s) of medication(s) given? 131 _____

   B. **Loss of specific motor skills such as standing, walking, running, etc.**

132 ____ yes ____ no ____ unknown

If yes, please describe _____

   C. **Bed wetting or soiling after 8 years of age.**

134 ____ yes ____ no ____ unknown ___ not 8 years old yet

2. **Has this patient ever had a head injury leading to unconsciousness or evaluation by a physician?**

____ yes ____ no ____ unknown

If yes, please describe _____

3. **Has the patient ever had a CT scan or MRI scan of the brain**

137 ____ yes ____ no ____ unknown

If yes, was it described to be abnormal? 138 ____ yes ____ no ____ unknown

Attention Deficit and Hyperactivity

1. **Has the patient ever been evaluated for attention deficit/hyperactivity disorder (ADD or ADHD)?**

139 ____ yes ____ no ____ unknown

If yes:

When was the evaluation done? Age: _____ Date: _____

Was the patient diagnosed with ADD or ADHD? 142 ____ yes ____ no ____ unknown

Was the patient ever treated for ADD or ADHD? ____ yes ____ no ____ unknown

What medications have been tried?

Drug	Dose	Ages	Response
144			147

University of Washington FAS Diagnostic & Prevention Network: NPIF8.doc 1/1/99 Patient Name:_____ 5

Mental Health Issues

1. Has the patient ever been evaluated by a psychiatrist, psychologist, or mental health counselor?

164 ____ yes ____ no ____ unknown

If yes, please list each psychiatrist, psychologist and/or counselor.

A. Type of professional: _____

Reason for assessment: _____

Type of therapy (i.e., behavioral, individual counseling, group counseling, family counseling, medicine): _____

_____

Age at the time of therapy: _____ Did the therapy help? ____ yes ____ no ____ unknown

If yes, how did it help? _____

_____

_____

B. Type of professional: _____

Reason for assessment: _____

Type of therapy (i.e., behavioral, individual counseling, group counseling, family counseling, medicine): _____

_____

Age at the time of therapy: _____ Did the therapy help? ____ yes ____ no ____ unknown

If yes, how did it help? _____

_____

_____

2. Has the patient ever been evaluated for mood problems (depression, anxiety, etc.) or phobia (fear)?

177 ____ yes ____ no ____ unknown

If yes:

When was the evaluation(s) done? Age(s): _____ Date(s): _____

What medications have been tried and how well did they work?

Drug	Dose	Response
_____	_____	
_____	_____	
_____	_____	
_____	_____	
_____	_____	

School Issues

1. **List ALL schools the patient has attended and the grades of attendance:**

School	City	Grades Attended	Received Special Education, Resource Room, Tutoring, etc. yes	no	unknown

2. **What learning problems does the patient have?**

3. **What behavioral problems does the patient have?**

University of Washington FAS Diagnostic & Prevention Network: NPIF8.doc 1/1/99 Patient Name:_____ 7

University of Washington FAS Diagnostic & Prevention Network: NPIF8.doc 1/1/99 Patient Name:_____ 8

Alcohol Exposure

Please fill in this information as completely as possible.
This information is critical to the evaluation of the patient.

Alcohol use by the birth mother

- **Before pregnancy:** average number of drinks per drinking occasion: 237_____
  maximum number of drinks per occasion: 238_____
  average number of drinking days per week: 239_____
  Type(s) of alcohol consumed: 244 ___wine, ___beer, ___ liquor, ___ unknown, ___ other (specify _____

- **During pregnancy:** average number of drinks per drinking occasion: 241_____
  maximum number of drinks per occasion: 242_____
  average number of drinking days per week: 243_____
  Type(s) of alcohol consumed: 244 ___wine, ___beer, ___ liquor, ___ unknown, ___ other (specify _____

Which trimester(s) did the mother drink alcohol? 245 _____ 1st _____ 2nd _____ 3rd _____ unknown

		No	Yes	Unknown
Was the birth mother ever diagnosed with alcoholism?	246	_____	_____	_____
Was the birth mother ever reported to have a problem with alcohol?	247	_____	_____	_____
Did the birth mother ever receive treatment for alcohol addiction?	248	_____	_____	_____

If the above information is unknown, please provide any information that might help describe the mother's level of alcohol use before and during pregnancy 249 _____

_____

_____

_____

Did the birth mother use any of the following substances during pregnancy?

Yes	No	Unknown	Type	Please List Specific Substance(s)	Month(s) of Pregnancy
250___	___	___	Drugs	251 _____	_____
254___	___	___	Tobacco	_____	_____
257___	___	___	Medications	258 _____	_____
___	___	___	X-rays	_____	_____

Information about the Patient's Biological Parents

Birth mother's name_____ Birth date 266 _____
First263 Middle264 Last265

Mother's Race 267 ❑ white ❑ black ❑ American Indian ❑ Alaskan Native ❑ Hispanic
❑ Asian ❑ unknown ❑ other (specify) _____

Education level attained (last year of school completed) 269 _____ Age at birth of patient 270 _____

Does she have a history of learning problems? 271 _____

Birth mother's Address _____
Street City273 State274 Zip275

When was the last contact with the birth mother? 276 _____

Birth father's name_____ Birth date 280 _____
First277 Middle278 Last279

Father's Race 281 ❑ white ❑ black ❑ American Indian ❑ Alaskan Native ❑ Hispanic
❑ Asian ❑ unknown ❑ other (specify) _____

Education level attained (last year of school completed) 283 _____ Age at birth of patient 284 _____

Does he have a history of learning problems? 285 _____

When was the last contact with the birth father? 286 _____

Medical History of the Biological Family

Has anyone in this patient's biological family ever had any of the following conditions? *Check all that apply.*

	Birth Mother	Birth Father	Mother's Family	Father's Family	Siblings of patient
Alcoholism 287					
Birth Defects 288					
Stillbirths 289					
Miscarriages 290					
Mental retardation 291					
Other developmental disabilities 292					
Learning disorders 293					
Attention deficit 294					
Hyperactivity 295					
Epilepsy 296					
Neurologic disease 297					
Child abuse 298					
Sexual abuse 299					
Depression 300					
Suicide 301					
Mental illness 302					
Vision problems 303					
Hearing problems 304					
Chronic illnesses 305					
Tourette syndrome 306					
Delinquency 307					
Any specific genetic condition 308					
Other 309					

University of Washington FAS Diagnostic & Prevention Network: NPIF8.doc 1/1/99 Patient Name:_____ 9

University of Washington FAS Diagnostic & Prevention Network: NPIF8.doc 1/1/99 Patient Name:_____ 10

Pregnancies of Birth Mother

1. Please list **all** of the birth mother's pregnancies including miscarriages, abortions, in the order of their occurrence:

Year	Length of Pregnancy	First name of child if applicable	Live born Child yes	Live born Child no	Normally Developed yes	Normally Developed no	If not "normally" developed, please explain *Include FAS / FAE diagnosis, if known*

Office Use:	402 Total Parity	403 Total Gravitity	404 Patient Parity	405 Patient Gravitity	406 FAS/FAE diagnoses

Pregnancy, Labor, and Delivery of this Patient

1. **Did the birth mother experience any difficulties during pregnancy?** 407 ___ Yes ___ No ___ Unknown

   If yes, please describe: _____

2. **Did the birth mother receive prenatal care?** 407a ___ Yes ___ No ___ Unknown
3. **Were there complications during the labor or delivery?** 409 ___ Yes ___ No ___ Unknown

   If yes, please explain: _____

4. **Was the delivery:** 411 _____ Natural _____ By C-section _____ Unknown

   Reason for C-Section, if performed _____

5. **Where was the patient born?** Hospital _____ City 414 _____ State 415 _____

6. **Apgar scores** 416 _____ at 5 minutes 417 _____ at 10 minutes

7. **How many days did the infant stay in the birth hospital?** 418 _____

8. **Did the patient have any of the following problems while still in the birth hospital?**

	Yes	No	Unknown		Yes	No	Unknown
Feeding problems	419 ___	___	___	Infections	422 ___	___	___
Apnea / breathing difficulties	420 ___	___	___	Jaundice	423 ___	___	___
Supplemental oxygen required	421 ___	___	___	Convulsions	424 ___	___	___

List of Professionals Currently Involved in Patient's Care

Primary Physician
Name: _____ Phone: _____
Address: _____

Other Physicians
Name: _____ Phone: _____
Specialty: _____
Address: _____

Name: _____ Phone: _____
Specialty: _____
Address: _____

Name: _____ Phone: _____
Specialty: _____
Address: _____

Mental Health Consultants *(includes Psychiatrists Psychologists, and Counselors)*
Name: _____ Phone: _____
Specialty: _____
Address: _____

Name: _____ Phone: _____
Specialty: _____
Address: _____

School
Name: _____ Phone: _____
Address: _____
Contact Person *(teacher, nurse, counselor, etc.)*: _____
_____

Other
Name: _____ Phone: _____
Profession: _____
Address: _____

University of Washington FAS Diagnostic & Prevention Network: NPIF8.doc 1/1/99 Patient Name: _____ 11

Placements

1. List all of the placements the patient has had from birth through today.

Type of placement (i.e., foster, adoptive, etc.)	Duration of placement	Age of patient when placement started

Office Use:	456 Total	457 First	458 Last

A. How long has the patient been in your care? 459_____

What to bring to Clinic

If the patient has had any of the following assessments, please bring them to Clinic on the day of your appointment. This information is very important to the patient's diagnostic evaluation.

_____ Photographs of the patient from birth to 10 years of age, without a smile.

_____ Medical records which document the problems you have reported above.

_____ School Assessments including:
- Achievement tests
- IQ tests
- Language assessments
- Social Skills assessments
- Behavior assessments

_____ Psychological Assessments

_____ Developmental Assessments including:
- Motor Development (fine and gross motor)
- Occupational Therapy assessments
- Mental (cognitive) assessments

Appendix B.

FAS-Tutor^{TM} CD-ROM

A CD-ROM entitled *Fetal Alcohol Syndrome-Tutor*^{TM} is available to accompany this Diagnostic Guide for FAS and Related Conditions. The CD-ROM provides additional instruction for medical professionals, through video, computer animation and photographic examples, on how to screen and diagnose FAS. Fetal Alcohol Syndrome-Tutor was supported by the March of Dimes Birth Defects Foundation.

To learn more about the CD-ROM, contact the

FAS Diagnostic and Prevention Network
Children's Hospital and Regional Medical Center
4800 Sand Point Way NE, CH-47
Seattle, WA, 98105

http://depts.washington.edu/fasdpn

Diagnostic Guide for FAS and Related Conditions Quick Reference Sheet

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DIAGNOSING THE FULL SPECTRUM OF FETAL ALCOHOL EXPOSED INDIVIDUALS: INTRODUCING THE 4-DIGIT DIAGNOSTIC CODE

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Abstract-The medical/research records of 1,014 patients diagnosed at the Washington State FAS Diagnostic and Prevention Network of clinics were used to develop a new, comprehensive, reproducible method for diagnosing the full spectrum of outcomes among patients with prenatal alcohol exposure. This new diagnostic method, called the 4-Digit Diagnostic Code, was compared to the standard gestalt method of diagnosis on the first 454 patients who had received a gestalt diagnosis of FAS, atypical FAS (AFAS) or possible fetal alcohol effect (PFAE) prior to the development of the 4-Digit Diagnostic Code. The outcomes of the patients were more accurately and comprehensively documented by the 4-Digit Diagnostic Code because of it's use of quantitative, objective measurement scales and specific case-definitions. The four digits in the Code reflect the magnitude of expression of the four key diagnostic features of FAS in the following order: (1) growth deficiency, (2) the FAS facial phenotype, (3) central nervous system damage/dysfunction, and (4) gestational alcohol exposure. The magnitude of expression of each feature is ranked independently on a 4-point Likert scale with 1 reflecting complete absence of the FAS feature and 4 reflecting a strong 'classic' presence of the FAS feature**.** The 4-Digit Diagnostic Code is being used effectively for diagnosis, screening and surveillance efforts in all Washington State FAS DPN clinics.

INTRODUCTION

The fetal alcohol syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. The definition of the FAS has changed little since the 1970's when the condition was first described and refined (Jones and Smith, 1973; Rosett, 1980; Clarren and Smith, 1978; Sokol and Clarren, 1989; Stratton *et al*., 1996). The syndrome has been broadly characterized by pre- and/or postnatal growth deficiency, a characteristic set of minor facial anomalies, central nervous system (CNS) dysfunction and prenatal alcohol exposure. The presentation of each individual feature of the syndrome may be variably expressed with age.

For trained clinicians, dysmorphologists, or clinical geneticists, there is likely to be full agreement on a diagnosis of FAS only when the anomalies in growth, face, and brain are all very extreme and the alcohol exposure is conclusive and substantial. But the features are not dichotomous, that is either normal or clearly abnormal. Rather, the features, and indeed the history of alcohol exposure, all range along separate continua from normal to clearly abnormal and distinctive.

In the absence of accurate, precise, and unbiased methods for measuring and recording the severity of exposure and outcome in individual patients, diagnoses will continue to vary widely from clinic to clinic (Chavez *et al*., 1988; Aase, 1994; Stratton *et al*., 1996). From a clinical perspective, diagnostic misclassification leads to inappropriate patient care, increased risk for secondary disabilities (Streissguth and Kanton, 1997) and missed opportunities for primary prevention. From a public health perspective, diagnostic misclassification leads to inaccurate estimates of incidence and prevalence (Stratton *et al*., 1996). Inaccurate estimates thwart efforts to allocate sufficient social, educational and health care services to this high-risk population and preclude accurate assessment of primary prevention intervention efforts. From a clinical research perspective, diagnostic misclassification reduces the power to identify clinically meaningful contrasts between groups. Non-standardized diagnostic methods prevent valid comparisons between studies.

The primary limitations in the current practice of diagnosing individuals with prenatal alcohol exposure include:

1. *While there are diagnostic guidelines that physicians and medical researchers are encouraged to follow, the guidelines are not sufficiently specific to assure diagnostic accuracy or precision.* While the diagnostic guidelines published by Sokol and Clarren (1989), which were a minor modification of the definition by the Fetal Alcohol Study Group of the Research Society for Alcoholism (Rosett, 1980) which, in turn, were derived from the work of Clarren and Smith (1978), do provide guidance, they are not sufficiently specific to assure diagnostic accuracy and precision. They reflect a more gestalt approach to diagnosis. The guidelines for CNS dysfunction do not address how many areas of deficit must be present, how severe the deficits must be or what level of documentation must exist to substantiate the presence of the deficit (i.e., parental history, psychometric testing or structural imaging). The guidelines for the facial phenotype are equally nonspecific. How many facial features must be present, how severe must the features be and what scale of measurement should be used to judge their severity? One need only read the clinical literature or review medical records, birth certificates, birth defect registries or ICD-9 codes to see how variably these criteria are interpreted, applied and reported (Cordero *et al*., 1994; CDC, 1995, 1995a; Ernhart *et al*., 1995; Stratton *et al*., 1996). Although the most recent guidelines published by the Institute of Medicine (Stratton *et al*., 1996) have not been out long enough to judge their impact on diagnostic accuracy and precision, the Institute guidelines present with the same limitations as previous guidelines.

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2. There is a lack of objective, quantitative scales to measure and report the magnitude of expression of key diagnostic features. For example, although a thin upper lip and smooth philtrum are key diagnostic features (Jones and Smith, 1973; Clarren and Smith, 1978; Astley and Clarren, 1996, Stratton *et al*., 1996), quantitative measurement scales have never been used to measure thinness or smoothness and guidelines have never been established for how thin or smooth the features must be. Objective quantitative scales would not only improve accuracy and precision, they would also greatly increase the statistical power to detect clinically important exposure-outcome patterns (Polit and Hungler, 1995) by increasing the level of measurement from the current nominal scales (e.g., upper lip thin/not thin) to ordinal scales (e.g., 5-point Likert pictorial scale for lip thinness) or continuous scales (e.g., upper lip circularity: perimeter^2/area). Ordinal and continuous scales better reflect the true continuum of outcome and exposure in FAS. Objective, quantitative scales also establish a common descriptive language for communicating outcomes in medical records and in the medical literature (Polit and Hungler, 1995).

3. The term fetal alcohol effects (FAE) is broadly used and poorly defined. The term 'suspected fetal alcohol effects' was first introduced into the medical literature in 1978 and was defined as 'less complete partial expressions' of FAS in individuals with prenatal alcohol exposure (Clarren and Smith, 1978). Based on this definition, an individual whose mother drank a few glasses of wine intermittently throughout pregnancy and presented with attention deficit hyperactivity disorder would meet the criteria for FAE. So would an individual whose mother drank a fifth of vodka (757ml) daily throughout pregnancy and presented with microcephaly, severe mental retardation, growth deficiency and no facial anomalies. The broad use of this term and the reluctance to abandon it points to the clear need to develop diagnostic terms for individuals with prenatal alcohol exposure who present with physical anomalies and/or cognitive/behavioral disabilities, but do not meet the criteria for FAS.

4. Clinical terms like FAE, alcohol related birth defects (ARBD) and alcohol related neurodevelopmental disorder (ARND) (Stratton et al. 1996) inappropriately imply a causal link between exposure and outcome in a given individual. With the likely exception of the full facial phenotype, no other physical anomalies or cognitive/behavioral disabilities observed in an individual with prenatal alcohol exposure are necessarily specific to (caused only by) their prenatal alcohol exposure (Stratton *et al*., 1996). There have already been formal appeals by noted dysmorphologists in the field to discontinue the use of the term FAE (Aase *et al*., 1995; Sokol and Clarren, 1989). The diagnostic terms ARBD and ARND introduce the same limitations as FAE, namely, implying alcohol exposure caused the birth defect or neurodevelopmental disorder in an *individual* patient.

5. The terms FAS and FAE fail to convey the diversity of disability present in these individuals. No two individuals with FAS present with precisely the same constellation of anomalies and disabilities. Growth, facial phenotype, CNS dysfunction and alcohol exposure all vary along separate continua. The term FAS only conveys that the condition is permanent and was caused by prenatal alcohol exposure. The term does not convey what the individual's disabilities are. A nomenclature that not only conveys the diversity of outcomes among individuals with prenatal exposure, but also separates outcome from exposure would benefit both the patient and their medical/social/educational care network.

Each of these limitations have been largely overcome with the development of a comprehensive manual for the diagnosis of FAS entitled '*Diagnostic Guide for Fetal Alcohol Syndrome and Related Conditions*' (Astley and Clarren 1999) introducing a new quantitative approach to diagnosis, the '4-Digit Diagnostic Code'. The diagnostic method was developed through the combined expertise of the University of Washington FAS Diagnostic and Prevention Network (FAS DPN) multidisciplinary, clinical team and the comprehensive records of 1,014 FAS DPN patients (birth to 51 years of age) with reported prenatal alcohol exposure.

The creation of the 4-Digit Diagnostic Code was developed to assure accurate and precise diagnosis of individuals with prenatal alcohol exposure across all seven FAS Clinics in the Washington State FAS DPN (Clarren and Astley 1997). The FAS DPN (expanded from the CDC-sponsored FAS Clinic at the University of Washington) was mandated by the 1995 Washington State Legislature in response to the high, statewide demand for diagnostic services. The guide was developed to meet the needs of a broad range of professionals in an equally broad range of settings. A core team that includes a physician, a psychologist, a language pathologist, an occupational therapist staffs each clinic and a family advocate. Each core team has community-based links to alcohol treatment centers, genetics clinics, schools, and social and legal service agencies. The seven clinics have been established in the following settings: a children's hospital neurodevelopmental clinic, two public health clinics, an alcohol treatment clinic, a private psychological services clinic paired with an academic institution and a comprehensive children's medical/social services center. These six clinics are led by the FAS DPN core center at the Center for Human Development and Disability at the University of Washington.

The need to standardize the criteria for FAS was recognized early on by the Fetal Alcohol Study Group of the Research Society of Alcoholism, resulting in a published guidelines by Rosett (1980) followed by several efforts to hone, clarify and express concern about the guidelines (Sokol and Clarren, 1989; Aase e. al., 1995; Stratton *et al*., 1996). In the absence of specific case-definitions, the FAS DPN has responded to both a mandate by its State legislature and recommendations by the Institute of Medicine (Statton *et al*., 1996) to establish a diagnostic method which could be administered accurately and reproducibly.

Below are a brief description of the 4-Digit Diagnostic Code and a comparison of the gestalt (Sokol and Clarren, 1989) and 4-Digit Diagnostic code outcomes for 454 patients seen in the FAS DPN who received both diagnostic approaches. A more detailed description of the 4-Digit Code can be found in a 111 page manual distributed by the University of Washington in Seattle. The diagnostic guide includes a standardized FAS Diagnostic and Evaluation Form accompanied by instructions, case definitions, normal anthropometric charts, pictorial Likert scales for ranking lip thinness and philtrum smoothness, and a New Patient Information Form which is completed by the patient's family to document the patient's exposure and developmental history. The guide is accompanied by an instructional CD-ROM entitled 'Fetal Alcohol Syndrome Tutor

Medical Training Software' (Astley *et al*., 1999). We have used the 4-Digit Code to diagnose over 1,000 patients and have found the system to be very helpful in clinical and research areas. We describe it here and present preliminary assessments of its accuracy, precision and power so that others can consider and evaluate its use.

METHODS

The 4-Digit Diagnostic Code was developed through the expertise of the multidisciplinary FAS DPN clinical staff and use of the medical research records of 1,014 patients diagnosed in the FAS DPN. The purpose was not to redefine, but rather, more specifically case define the key diagnostic components of FAS as presented across several published FAS diagnostic guidelines (Clarren and Smith, 1978; Rosett, 1980; Sokol and Clarren, 1989; Stratton *et al*., 1996). The first working draft of the method completed in 1997 (Astley and Clarren, 1997), was pilot tested on all patients seen in the FAS DPN from 1997 – 1999 ($n \approx 400$) and was refined to its current form. Prior to the development of the 4-Digit Code, all 598 patients seen in the University of Washington FAS DPN Clinic (1993-97) were diagnosed using the 'gestalt' (Sokol and Clarren, 1989) method. In 1997, the FAS DPN clinics stopped using the gestalt method and started using the 4-Digit Diagnostic Code method. The charts of all patients who had previously been diagnosed with the gestalt method were retrofitted to the 4-Digit Diagnostic Code system for research purposes. The gestalt and 4-Digit Diagnostic Code outcomes are compared among the 454 patients who had received gestalt diagnoses of FAS, atypical FAS (AFAS) or possible fetal alcohol effect (PFAE). The University of Washington Human Subjects Review Board approved use of this data.

Preliminary assessments of precision, accuracy and power are presented to assist the reader in their evaluation of this new diagnostic method. The diagnostic evaluation forms of 20 patients were randomly selected from the 736 patients who received a 4-Digit Diagnostic Code one to four years ago at the University of Washington FAS DPN Clinic by SKC and SJA. The standardized diagnostic forms document the clinical and psychometric data that was available on the patient at the time of their diagnosis. The 4-Digit Codes were deleted from the forms by the research assistant and re-derived by SKC and SJA independently. Inter-rater reliability between SKC and SJA was assessed by comparing their re-derived 4-Digit Codes. Intra-rater reliability was assessed by comparing the re-derived codes to the original 4-Digit Codes. An additional assessment of inter-rater reliability was conducted on all 16 patients who had received 4-Digit Diagnostic Codes from one of the six FAS DPN clinics without consult by the FAS DPN Core team at the University of Washington. The level of agreement between the 4-Digit Diagnostic Codes derived by the Network and University of Washington clinical teams was assessed. The Kappa statistic was computed to test intra-and inter-rater agreement. Accuracy (the degree to which a measurement represents the true value of the attribute that is being measured) was assessed by comparing the 4-Digit Diagnostic outcomes to the gestalt diagnostic outcomes of the 454 patients who were diagnosed by both methods. Each of the diagnostic outcomes were also compared to the published diagnostic guidelines (Sokol and Clarren, 1989) available when the gestalt diagnoses were made. Power, the probability of detecting an effect in a study sample if an effect of a specified size or greater truly exists in the population was computed using SamplePower (SPSS Inc., 1997).

RESULTS

The 4-Digit Diagnostic Code

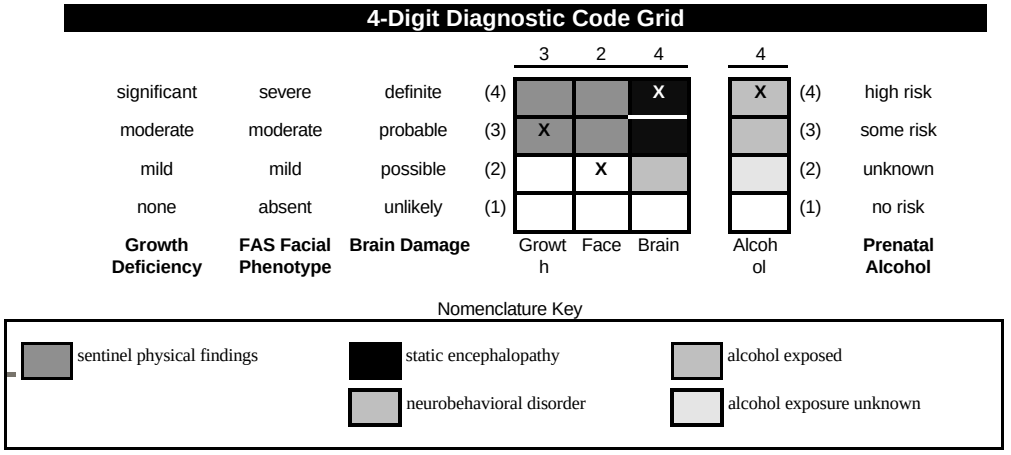
The four digits of the diagnostic code reflect the magnitude of expression of four key diagnostic features of FAS in the following order: (1) growth deficiency, (2) the FAS facial phenotype, (3) brain damage/dysfunction, and (4) gestational alcohol exposure (Fig. 1). The 4-Digit Diagnostic Code is generated by first recording key clinical data on the standardized FAS Diagnostic Evaluation Form and following specific case-definitions to generate each digit.

The magnitude of expression of each feature is ranked independently on a 4-point Likert scale with 1 reflecting complete absence of the FAS feature and 4 reflecting a strong 'classic' presence of the FAS feature. Each Likert rank is specifically case-defined. The 4-Digit Diagnostic Code can be used to diagnose individuals of all ages.

Clinical Nomenclature

There are 256 possible 4-Digit Diagnostic Codes ranging from 1111 to 4444. Each 4-Digit Diagnostic Code falls into one of 22 unique Clinical Diagnostic Categories (labeled A through V) (Table 1). The 22 Diagnostic Categories are named to reflect the Likert ranking of each digit in the 4-Digit Diagnostic Code. The names are constructed sequentially from four terms: 'sentinel physical findings', 'neurobehavioral disorder', 'static encephalopathy' and 'alcohol exposure status' as presented in Figure 1 and Table 1. Note that the names for Diagnostic Categories E-J, K-P and Q-V only differ by alcohol exposure, thus there are essentially only nine unique diagnostic *outcome* categories ranging from 'no cognitive/behavioral or sentinel physical findings detected' to 'FAS'. This is in contrast to the five diagnostic outcome categories (FAS, Partial FAS, ARBD, ARND and FAE) currently in use across the various gestalt guidelines (Clarren and Smith, 1978; Sokol and Clarren, 1999; Stratton *et al*., 1996).

The first two diagnostic categories (A and B) meet the criteria for a clinical diagnosis of FAS and are named as such (Table 1). The term Atypical FAS (category C) is introduced for use with a relatively small group of patients who present with static encephalopathy, most, but not all of the sentinel physical findings of FAS, and were alcohol exposed. The term FAS Phenocopy (category D) applies to the patient who presents with all of the features of FAS, but has a confirmed *absence* of gestational ethanol exposure. We have not yet observed such a patient. The remaining 19 categories (E - V) do not meet the minimum criteria for FAS and are subsequently named to reflect the Likert ranking of each digit in the 4-Digit Diagnostic Code. For example, a code of 4342 is the Diagnostic Category called '*sentinel physical findings / static encephalopathy (alcohol exposure unknown)*'. Many of these patients might have previously been referred to variably as having possible ARBD), or alcohol related neurodevelopmental disorder ((ARND) (Stratton *et al*., 1996).



4-Digit Diagnostic Code Grid and Nomenclature
This grid is used to record the 4-Digit Diagnostic Code following the guidelines presented in the text. A code of 3 or 4 in the Growth or Face column is referred to as a 'sentinel physical finding'. A code of 2 in the Brain column is a 'neurobehavioral disorder'; a code of 3 or 4 is 'static encephalopathy'. A code of 3 or 4 in the alcohol column is 'alcohol exposed'. The code 3244 would receive the name 'sentinel physical findings, static encephalopathy, alcohol exposed'. A subset of 4-Digit Diagnostic Codes that fall within the category 'sentinel physical findings, static encephalopathy, alcohol exposed' are referred to as FAS when the four digits are sufficiently high to meet the criteria for FAS (see Table 1).

This new nomenclature replaces all of these terms. These terms are not used here because the inclusion of 'alcohol-related' or 'alcohol-effect' in the diagnostic name inappropriately implies a confirmed causal link between exposure and outcome in an individual. Diagnostic Categories E - I would have previously been referred to as 'fetal alcohol effects', 'alcohol related birth defects' or 'alcohol related neurobehavioral disorder'. Categories J - V are new categories that describe a large number of patient groups who have never been adequately classified or described in the past. The Likert ranks for the four digits of the code are case defined for consistent application. The case definitions are briefly presented below and are more fully presented in the Diagnostic Guide for FAS (Astley and Clarren, 1999).

Case Defining the Growth Component of the 4-Digit Diagnostic Code

Age- and gender- adjusted height- and weight-centiles are ranked by circling A, B or C in the ABC-Score table (Table 2A). The Height-Weight ABC Score recorded in Table 2A is converted to a 4-Digit Diagnostic Code Rank using Table 2B. The 4-Digit Code Rank is transferred to the 4-Digit Diagnostic Code Grid (Figure 1). Detailed instructions are provided in the Diagnostic Guide for FAS (Astley and Clarren, 1999) for ranking growth when growth measures are available at more than one time point.

Case Defining the Facial Phenotype Component of the 4-Digit Diagnostic Code

Three key diagnostic features characterize the FAS facial phenotype: small palpebral fissures, a smooth philtrum and thin upper lip (Clarren and Smith, 1978; Astley and Clarren, 1996). Palpebral fissure length z-scores are computed with adjustment for age and when possible, race (Hall *et al*., 1989). The thinness of the vermilion border of the upper lip and the smoothness of the philtrum are coded independently on 5-point pictorial Likert scales using Figure 2. Lips must be gently closed with no smile. The magnitude of palpebral fissure length deficiency, philtrum smoothness and upper lip thinness are ranked by circling A, B, or C in each column in the ABC-Score table (Table 3A). The ABC-Score is converted to the 4-Digit Diagnostic Code Rank for face using Table 3B.

Facial phenotype can be assessed directly or from digitized facial photographs (Astley and Clarren, 1996; Astley *et al*., 1999). It has been our experience that palpebral fissure length and upper lip thinness can be more accurately measured from digitized photographs using image analysis software (SigmaScan, 1996). A standardized, digital, facial photograph is taken of the patient with an internal measure of scale (2 cm sticker) placed on the forehead. The image is displayed on a computer monitor and PFL is measured by clicking the mouse on the endocanthion and exocanthion landmarks and comparing the distance between the landmarks relative to the size of the internal measure of scale. Upper lip thinness is measured by tracing the outline of the vermilion border with the mouse and computing circularity (perimeter^2/area). The thinner the lip the smaller the circularity. Circularity is used to guide the 5-point ranking of upper lip thinness as demonstrated in Figure 2. All patients seen in the FAS DPN clinic have their digital facial photographs analyzed during their diagnostic evaluation. The process takes approximately ten minutes and is described in detail in the FAS Tutor™ CD-ROM (Astley *et al*., 1999).

Table 1. Diagnostic Categories.

Category	Diagnostic Category Name and 4-Digit Codes within each Category
A	Fetal alcohol syndrome (alcohol exposed)
	3433 4433 3434 4434 3443 4443 3444 4444
B	Fetal alcohol syndrome (alcohol exposure unknown)
	3432 4432 3442 4442
C	Atypical fetal alcohol syndrome (alcohol exposed)
	1443 1434 2434 3334 4334 2443 1444 2444 3344 4344 4343
D	Fetal alcohol syndrome phenocopy (no alcohol exposure)
	3431 4341 4441 3441 4431
E	Sentinel physical findings / static encephalopathy (alcohol exposed)
	1333 1433 2344 3143 3243 4133 4233 4333 1334 2333 2433
	3144 3244 4134 4234 1343 2334 3133 3233 3333 4143
	4243 1344 2343 3134 3234 3343 4144 4244
F	Static encephalopathy (alcohol exposed)
	1133 1144 1243 2134 2233 2244 1134 1233 1244 2143 2234
	1143 1234 2133 2144 2243
G	Sentinel physical findings / neurobehavioral disorder (alcohol exposed)
	1323 2323 3123 3323 4123 4323 1324 2324 3124 3324 4124
	4324 1423 2423 3223 3423 4223 4423 1424 2424 3224 3424
	4224 4424
H	Neurobehavioral disorder (alcohol exposed)
	1123 2123 1124 2124 1223 2223 1224 2224
I	Sentinel physical findings (alcohol exposed)
	1313 2313 3113 3313 4113 4313 1314 2314 3114 3314 4114
	4314 1413 2413 3213 3413 4213 4413 1414 2414 3214 3414
	4214 4414
J	No cognitive/behavioral or sentinel physical findings detected (alcohol exposed)
	1113 2113 1114 2114 1213 2213 1214 2214
K	Sentinel physical findings / static encephalopathy (alcohol exposure unknown)
	1332 2332 3132 3332 4232 1342 2342 3142 3342 4242 1432
	2432 3232 4132 4332 1442 2442 3242 4142 4342
L	Static encephalopathy (alcohol exposure unknown)
	1132 1232 2132 2232 1142 1242 2142 2242
M	Sentinel physical findings / neurobehavioral disorder (alcohol exposure unknown)
	1322 2322 3122 3322 4122 4322 1422 2422 3222 3422 4222
	4422
N	Neurobehavioral disorder (alcohol exposure unknown)
	1122 1222 2122 2222
O	Sentinel physical findings (alcohol exposure unknown)
	1312 2312 3112 3312 4112 4312 1412 2412 3212 3412 4212
	4412
P	No cogn./behavioral or sentinel physical findings detected (alcohol exposure unknown)
	1112 2112 1212 2212
Q	Sentinel physical findings / static encephalopathy (no alcohol exposure)
	1331 2341 3231 4141 1341 2431 3241 4231 1431 2441 3331
	4241 1441 3131 3341 4331 2331 3141 4131
R	Static encephalopathy (no alcohol exposure)
	1131 2131 1141 2141 1231 2231 1241 2241
S	Sentinel physical findings / neurobehavioral disorder (no alcohol exposure)
	1321 3121 4121 1421 3221 4221 2321 3321 4321 2421 3421
	4421
T	Neurobehavioral disorder (no alcohol exposure)
	1121 2121 2221 1221
U	Sentinel physical findings (no alcohol exposure)
	1311 3111 4111 1411 3211 4211 2311 3311 4311 2411 3411
	4411
V	No cognitive/behavioral or sentinel physical findings detected (no alcohol exposure)
	1111 2111 1211 2211

The 4-Digit Diagnostic Code reflects the magnitude of expression of four key diagnostic components of FAS in the order growth, facial phenotype, CNS damage/dysfunction and alcohol exposure. Each component is measured on a 4-point Likert scale, thus producing 256 possible combinations of 4-Digit Diagnostic Codes. These codes are collapsed into 22 Diagnostic Categories as presented above

Case-Defining the Brain Damage/Dysfunction Component of the 4-Digit Diagnostic Code

Brain damage/dysfunction is the most significant disability for individuals damaged by prenatal alcohol exposure. Ethanol alters the developing brain in a variety of ways from structural to gross anomalies of gray and/or white matter and/or to subtle alterations in neurochemical levels (West, 1986). Accurately quantifying and qualifying brain damage/dysfunction

Table 2. ABC score and case definitions for growth deficiency

A)

ABC Rank	Centile Range	Circle the ABC-Score for: Height	Weight
C	≤ 3rd	C	**C**
B	>3rd and ≤ 10th	**B**	B
A	>10th	A	A

B)

4-Digit Diagnostic Code Rank	Growth Deficiency Category	Height-Weight ABC-Score Combinations
4	Severe	CCC
3	**Moderate**	CB, **BC**
2	Mild	CA, BB, AC
1	None	BA, AB, AA

A) The first step in deriving the Likert rank for growth is to derive the ABC-Score for growth. If a patient's height centile was 8% and weight centile was 2%, an ABC-Score of **BC** would be assigned. B) The final step in deriving the Likert rank for growth is to convert the ABC-Score for Growth into a 4-Digit Diagnostic Code rank. A score of **BC** translates into a 4-Digit Diagnostic Code rank of **3.** This rank would serve as the first digit in the 4-Digit Diagnostic Code (Figure 1).

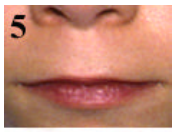
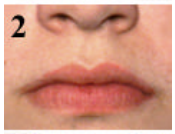
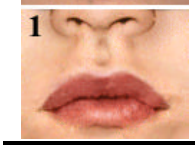
Lip-Philtrum Guide Likert Ranks	ABC-Score	Upper Lip Circularity
	C	178
	C	80
	B	65
	A	50
	A	35

Figure 2. Lip-Philtrum Guide

Pictorial examples of the 5-point Likert scale, upper lip circularity scale and the ABC-scale used to rank upper lip thinness and philtrum smoothness. Circularity (perimeter^2/area) is a continuous measure of upper lip thinness that can be used to facilitate the ranking of the upper lip. Circularity ranges from 12.8 for a circle to infinity as the circle is squashed into a line (or becomes thinner). Circularity is measured by outlining the vermilion border of the upper lip using image analysis software such as SigmaScan Pro (1996) (Astley and Clarren, 1996; Astley *et al*., 1999). It is important that the individual's lips are gently closed with no smile.

is important for both diagnosis and treatment planning. Brain damage can be defined in a large number of ways that are each associated with a broad spectrum of disability. The 4-point Brain Damage Likert Scale (Table 4) allows the clinician to separate patients with clear evidence of brain damage (Likert Rank 4) from patients with no evidence of brain damage (Likert Rank 1). The 4-Digit Rank for brain does not rank the severity of structural, neurologic or functional problems faced by the patient. Rather it ranks the strength of evidence supporting the presence of an organic cause for cerebral/cerebellar dysfunction.

A rank of 4 is reserved for patients who present with 'medical' evidence of structural or neurologic brain damage. Examples include any one of the following: microcephaly, structural alterations on brain imaging studies, hard neurologic findings like a primary seizure disorder or cerebral palsy or an intelligence quotient that is clearly below the normal distribution (FSIQ<60).

A rank of 3 is reserved for patients who present with 'psychometric' evidence of brain damage. Clearly, there are patients who have organic brain damage at a level not detectable by the current technology that allows us to derive a Rank 4. In the absence of advanced technology, we feel it is important to identify patients who present with cognitive/behavioral dysfunction as measured on standardized psychometric tests. At this time we case define Rank 3 to mean that a patient has had an age appropriate battery of tests in the areas of intelligence, adaptation, academic achievement, language and neuropsychology. The pattern of abnormality on the test battery, when taken as a whole, must be clinically interpreted by the assessing team to strongly support abnormal brain function. Patients who do not meet the

Table 3. ABC score and case definitions for facial phenotype

A)

5-Point Likert Scale for Philtrum & Lip	Z-score for largest Palpebral Fissure Length	Palpebral Fissure	Circle the ABC-Scores for: Philtrum	Upper Lip
4 or 5	≤ -2 SD	C	C	C
3	>-2 SD and ≤ -1 SD	B	B	B
1 or 2	> -1 SD	A	A	A

B)

4-Digit Diagnostic Code Rank*	Level of Expression of FAS Facial Phenotype	Palpebral Fissure - Philtrum - Lip ABC-Score Combinations
4	Severe	CCC
3	Moderate	CCB, CBC, BCC
2	**Mild**	CCA, CAC, CBB, CBA, **CAB**, CAA BCB, BCA, BBC, BAC ACC, ACB, ACA, ABC, AAC
1	Absent	BBB, BBA, BAB, BAA ABB, ABA, AAB, AAA

A) The first step in deriving the Likert rank for facial phenotype is to derive the ABC-Score for facial phenotype. If a patient's palpebral fissure lengths were > 2 SD below the norm and their philtrum and upper lip received Likert scores of 2 and 3 respectively (Figure 2), the facial phenotype would receive an ABC-Score of **CAB**. B) The final step in deriving the Likert rank for facial phenotype is to convert the ABC-Score for Facial Phenotype to a 4-Digit Diagnostic Code Rank. A **CAB** score translates into a 4-Digit Diagnostic Code rank of **2**. This rank would serve as the second digit in the 4-Digit Code (Figure 1).

Table 4. Case Definitions for Brain Damage.

4-Digit Diagnostic Code Rank	Brain Damage Scale	Confirmatory Findings
4	**Definite** *referred to as static encephalopathy*	● **Microcephaly, OFC ≤ -2 S. D.** *and / or* ● Abnormalities on brain images diagnostic of prenatal alteration *and / or* ● Evidence of persistent neurologic findings likely to be of prenatal origin *and / or* ● I.Q. score ≤ 60
3	**Probable** *referred to as static encephalopathy*	● Substantial deficiencies or discrepancies across multiple areas of brain performance such as cognition, achievement, adaptation, neurologic 'soft' signs, and language. Three or more areas should be found aberrant.
2	**Possible** *referred to as neurobehavioral disorder*	● Historical information / personal observations strongly suggest that the possibility of brain damage, but data to this point does not permit a Rank 3 or 4 classification.
1	**Absent**	● No problems likely to reflect brain damage are presented.

A patient presenting with a head circumference below the second centile would receive a 4-Digit Diagnostic Code rank of **4**. This rank would serve as the third digit in the 4-Digit Code (Figure 1).

criteria for a Rank 4, yet have psychometric test outcomes that document abnormal brain function (greater than 2 standard deviations below the mean) across three or more areas listed above receive a Rank 3. Although there are no scientific data to support that a criterion of three or more failures is more reflective of brain damage than a criterion of one or two failures, our experience with over 1,000 patients has demonstrated that the criteria we have selected have good face validity (e.g., the team is more likely to clinically interpret the battery as a whole as strongly supporting abnormal brain function when there are three or more failures). We anticipate that further clinical research coupled with rapidly advancing technology will likely provide more objective scientific data from which to judge the validity of these criteria. It is important to note that it is possible for a patient to meet the criteria for both a Rank 3 and Rank 4 since these are not mutually exclusive categories. If this occurs, the higher rank (Rank 4) is inserted into the 4-Digit Code because, for diagnostic purposes, it reflects the strongest clinical evidence of brain damage. The psychometric outcomes, whether normal or abnormal, facilitate the development of the treatment plan for all patients.

Likert Rank 2 is given to two subgroups of patients. All patients in Rank 2 should have histories of behavioral and/or cognitive problems that strongly suggest underlying brain dysfunction. One group of patients has not yet had the types of testing that would move them into Ranks 3 or 4, if positive. The reason for

Table 5. Case Definitions for Prenatal Alcohol Exposure.

4-Digit Diagnostic Code Rank	Prenatal Alcohol Exposure Category	Description
4	**High Risk**	● Alcohol use during pregnancy CONFIRMED *and* ● Exposure pattern is consistent with the medical literature placing the fetus at 'high risk' (generally high peak blood alcohol concentrations delivered at least weekly in early pregnancy).
3	Some Risk	● Alcohol use during pregnancy CONFIRMED *and* ● Drinking occurred in gestation in frequencies and volumes less than in Rank 4 or exact amounts unknown.
2	Unknown Risk	● Gestational exposure is simply not known or information is of questionable reliability.
1	No Risk	● Alcohol use during pregnancy is CONFIRMED to be completely ABSENT.

The case-definitions used to derive the 4-Digit Diagnostic Code rank for alcohol exposure. If a birth mother reported drinking a fifth of liquor several times a week throughout pregnancy, alcohol exposure would receive a 4-Digit Diagnostic Code rank of **4**. This rank would serve as the fourth digit in the 4-Digit Code (Figure 1).

this lack of testing is usually because the patients are too young to be reliably or conclusively tested (i.e., less than six years of age). The other group of patients is those who have had testing that did not reveal compelling evidence for Rank 3 or 4 classification, and yet, in the clinician's judgment, a strong possibility of brain damage can not be wholly dismissed. Alternative testing and/or follow-up testing should usually be considered. If adequately sensitive and appropriate testing has been carried out without clear evidence of brain dysfunction, it is unlikely a Rank 2 classification would be given.

Patients are classified as Rank 1 when no structural, neurological or cognitive/behavioral problems measured by clinical/psychometric assessment or caregiver interview are discerned.

Case Defining the Gestational Alcohol Exposure Component of the 4-Digit Diagnostic Code

Alcohol exposure is ranked according to the quantity, timing, frequency and certainty of exposure during pregnancy (Table 5). The case-definitions address the facts that exposure information is often unavailable and/or inaccurate and a clear consensus is not available concerning the amount of alcohol that can actually be toxic to each individual fetus (Stratton *et al.*, 1996). The case-definitions differentiate four clinically meaningful exposure groups (4. confirmed high exposure, 3. confirmed exposure, but level is low or unknown, 2. unknown exposure, and 1. confirmed absence of exposure).

High exposure is defined generally to be a blood alcohol concentration of greater than 100 mg/dL (a level that typically can be reached by a 55-kg woman consuming six to eight beers) weekly, early in pregnancy. In the absence of a clear consensus on the amount of alcohol that can actually be toxic to the fetus, this general definition should only serve as a guide, not a threshold. One example of a 'rank 4' exposure is birth mother reported drinking to intoxication weekly throughout pregnancy. Two examples of 'rank 3' exposures include: a) birth mother was observed to be drinking during pregnancy, but the amount is unknown, b) birth mother reported drinking one glass of wine once a week, but stopped drinking as soon as she learned she was pregnant. A few examples of when alcohol exposure is ultimately unknown and thus coded as a 'rank 2' include: a) the child is adopted and the records are closed, b) birth father reports birth mother drank while pregnant, but birth mother

Table 6. Cross-tabulation of Gestalt and 4-Digit Diagnostic Outcomes.

4-Digit Diagnostic Categories		Gestalt Diagnostic Categories FAS n = 69	AFAS n = 41	PFAE n = 344	Total n = 454
A	FAS (AE)	8	2	0	10
B	FAS (AE Unknown)	1	0	0	1
C	Atypical FAS (AE)	12	2	2	16
E	Sentinel physical findings/static encephalopathy (AE)	10	10	17	37
F	Static encephalopathy (AE)	8	8	69	73
G	Sentinel physical findings/neurobehavioral disorder (AE)	15	11	15	41
H	Neurobehavioral disorder (AE)	11	7	179	197
I	Sentinel physical findings (AE)	0	1	6	7
J	No cognitive/behavioral or sentinel physical findings (AE)	0	1	18	19
K	Sentinel physical findings /static encephalopathy (AE unknown)	1	0	2	3
L	Static encephalopathy (AE unknown)	0	1	5	6
M	Sentinel physical findings /neurobehavioral disorder (AE unknown)	2	0	5	7
N	Neurobehavioral disorder (AE unknown)	1	0	25	26
P	No cognitive/behavioral or sentinel physical findings (AE unknown)	0	0	1	1

Cross-tabulation of the Gestalt and 4-Digit diagnostic outcomes for 454 patients diagnosed by both methods in the Washington State FAS DPN clinics.
AE, alcohol exposure during gestation confirmed; AE unknown, alcohol exposure during gestation unknown; FAS, fetal alcohol syndrome; AFAS, atypical fetal alcohol syndrome; PFAE, possible fetal alcohol effects.

Table 7. Comparison of Gestalt and 4-Digit Diagnostic Outcomes.

4-Digit Ranks for Key	Diagnostic Outcomes						
	FAS		AFAS		PFAE		All Other
Diagnostic Features	Gestalt	4-Digit[1]	Gestalt	4-Digit[2]	Gestalt	4-Digit[3]	4-Digit[4]
	n = 69	n = 11	n = 41	n = 16	n = 344	n = 365	n = 62
Growth Deficiency[5] (n)							
1. None	37	0	28	8	295	295	57
2. Mild	10	0	1	2	24	31	2
3. Moderate	8	3	5	2	11	17	2
4. Significant	14	8	7	4	14	22	62
FAS Facial Phenotype[6] (n)							
1. Absent	0	0	1	0	71	60	12
2. Mild	27	0	21	0	247	253	43
3. Moderate	15	0	11	6	20	36	4
4. Severe	27	11	8	10	6	17	3
Brain Damage[7] (n)							
1. Unlikely	0	0	2	0	25	7	20
2. Possible	29	0	18	0	224	238	33
3. Probable	13	2	9	7	44	53	4
4. Definite	27	9	12	9	51	67	5
Prenatal Alcohol Exposure[8] (n)							
1. No0	0	0	0	0	0	0	
2. Unknown	5	1	1	0	38	0	43
3. Some risk	26	5	17	2	160	188	8
4. High risk	38	5	23	14	146	177	11

Magnitude of expression of key FAS diagnostic features compared between the gestalt (Sokol and Clarren, 1989) and 4-Digit (Astley and Clarren 1999) diagnostic outcomes of 454 patients diagnosed by both methods in the Washington State FAS DPN clinics

FAS: fetal alcohol syndrome; AFAS: atypical fetal alcohol syndrome; PFAE: possible fetal alcohol effects; (1) 4-Digit Diagnostic categories A and B; (2) 4-Digit Diagnostic Category C; (3) 4-Digit Diagnostic Categories E-I; (4) All other 4-Digit Diagnostic Categories D, J-V; (5) Defined in Tables 2A, 2B; (6) Defined in Tables 3A and 3B; (7) Defined in Table 4; (8) Defined in Table 5.

reports she did not drink, c) birth mother started drinking at the age of 13 yrs, was never known to have a prolonged period of sobriety, thus the family assumed she drank during pregnancy.

Other Prenatal and Postnatal Exposures/Experiences

A comprehensive diagnostic process must take into consideration the risks associated with prenatal and postnatal exposures and experiences other than prenatal alcohol exposure. Most of the features associated with FAS are not specific to prenatal alcohol exposure. A variety of prenatal (poor prenatal care, prenatal complications, familial genetics and exposure to other potentially teratogenic agents, etc.) and/or postnatal (physical/sexual abuse, disrupted placement histories, head injuries, chronic substance abuse by the patient, etc.) events could explain all or some of the symptoms presented by the patient. The 4-Digit Diagnostic method requires the clinician to record pertinent prenatal and postnatal exposures and events on the standardized FAS Diagnostic Evaluation Form, rank their severity using case-defined 4-point Likert scales and report them in the standardized medical summary template provided in the Diagnostic Guide for FAS (Astley and Clarren, 1999).

Comparison of the Gestalt and 4-Digit Diagnostic Methods

The gestalt (Sokol and Clarren, 1989) and 4-Digit Diagnostic Code outcomes for 454 patients who initially received gestalt diagnostic evaluations at the University of Washington FAS DPN clinic are compared in Tables 6 and 7. Table 6 presents a cross-tabulation of the gestalt and 4-Digit diagnostic outcomes. Table 7 illustrates the variable magnitude of expression of the key diagnostic features of FAS (growth, face, brain and alcohol) for the three gestalt diagnostic outcomes (FAS, PFAS and PFAE) and for the equivalent 4-Digit diagnostic categories (Categories A and B are equivalent to the gestalt FAS; Category C is equivalent to the gestalt PFAS; and Categories E - I would be equivalent to the gestalt category of PFAE). The study population was 57.7% male, ranged in age from birth to 51 years old with a mean of 10.1 ± 7.0 years and had the following racial distribution: Caucasian (57.5%), African American (9.0%), Native American/Alaskan (14.1%), other (19.4%). Race, age and gender were equally distributed across the 4-Digit and gestalt diagnostic categories.

Of the 69 patients who received a gestalt diagnosis of FAS, only nine met the 4-Digit criteria for FAS (Categories A and B) (Table 6). In the absence of specific case-definitions, quantitative measurement scales and only three diagnostic choices (FAS, PFAS, or PFAE), the gestalt method for diagnosing FAS produced a very heterogeneous population, more heterogeneous than would be supported by the gestalt guidelines (Sokol and Clarren, 1989). For example, 37 of the 69 patients had no evidence of growth deficiency, 27 had only one of the three facial features, 29 had no psychometric or structural evidence of brain damage and five had unknown exposure to
alcohol (Table 7). Of the 344 patients who received a gestalt diagnosis of PFAE, the outcomes of these patients are also remarkably variable. These patients fall into 13 different 4-Digit

Diagnostic Categories (Table 6) and present with every combination of diagnostic features (Table 7). The term PFAE clearly fails to convey the diversity of outcomes within this group. Some patients received a diagnosis of PFAE based solely on alcohol exposure (n = 18) while other patients received a diagnosis of PFAE based on outcomes that fell just short of the full syndrome (n = 2). Research studies that treat this diverse group of patients as one 'homogeneous' group are at great risk of failing to identify clinically meaningful outcomes.

Precision: Inter- and Intra-rater Reliability

The 4-Digit Diagnostic Codes of 20 randomly selected patient files were rederived by SKC and SJA independently while masked to the original 4-Digit code that had been derived one to four years ago by the University of Washington Clinical team. The codes re-derived by SKC and SJA matched the original 4-Digit Codes across all four digits for all 20 subjects (inter- and intra-rater reliability was 100%, (Kappa = 1.0, p = 0.000). The 4-Digit Codes for the 20 randomly selected patients spanned the entire spectrum of normal to AFAS (1124 to 1444). Inter-rater reliability between the six FAS DPN regional clinics and the University of Washington FAS DPN Core clinic resulted in an exact match across all four digits on 15 of 16 (94%) patients (Kappa = 0.93, p = 0.000) and an exact match on Diagnostic Category on all 16 (100%) of the patients (Kappa = 1.0, p = 0.000). The one 4-Digit code that did not match was coded by the regional FAS DPN clinic as 1223 and the University FAS DPN clinic as 1123. The mismatch in the facial score was due to the network physician not pulling the epicanthal fold back before measuring the palpebral fissure length resulting in an underestimate of the length.

POWER

To demonstrate the statistical power of the 4-Digit Code over the gestalt method of diagnosis, the hypothesis that the full-scale intelligence quotient (FSIQ) decreases with increasing magnitude of expression of the FAS facial phenotype was tested among 216 patients who had been diagnosed by both the gestalt and 4-Digit diagnostic systems. Of the 216 patients, 31 received a gestalt diagnosis of FAS. The difference in the mean FSIQ between the patients with and without the gestalt FAS facial phenotype (82.3 and 85.0 respectively) was not statistically significant (t = -1.56, p = 0.13). In contrast, when the same 216 patients were classified by their 4-point Likert rank reflecting the magnitude of expression of the FAS facial phenotype, a statistically significant, inverse, linear association was revealed. The mean FSIQ among the patients with Likert facial ranks of 4, 3, 2, and 1 were 78.5, 83.8, 84.8 and 87.7 respectively (f = 4.1, p = 0.04). The power of the t-test to detect a contrast in facial phenotype between the two gestalt groups was only 23%, whereas the power of the ANOVA to detect the linear trend was 85%. By convention, the minimum power of a clinical research study is set at 80% (Hulley and Cummings, 1988). Thus, a clinically important linear association between face and brain that was detected by the 4-Digit Code failed to be detected by the gestalt method of diagnosis.

DISCUSSION

The 4-Digit Diagnostic Code method has been used in all seven FAS DPN clinics in Washington State for over three years, demonstrating that it can be taught to a broad array of social and health care professionals in an equally broad array of clinical settings. Some of our FAS DPN colleagues were hesitant to make diagnoses in patients with prenatal alcohol exposure prior to using this system precisely because the old nomenclature was too simplistic and did not offer consistent or helpful diagnostic outcomes. After three years of field testing this method, both prospectively and retrospectively on over 1,000 patients, it continues to uniformly reflect clinical judgement (a measure of face validity) and provide tremendous power to identify clinically meaningful patterns of outcome.

The 4-Digit Diagnostic Code presents with many strengths. It offers an intuitively logical digital approach to reporting outcomes and exposure that reflects the true diversity and continuum of disability associated with prenatal alcohol exposure. Preliminary assessments of precision, accuracy and power appear to be greatly increased over the 'gestalt' method of diagnosis. This can be attributed, in large part, to the use of objective, ordinal and continuous measurement scales, specific, comprehensive case-definitions (Polit and Hungler, 1995) and the use of a multidisciplinary clinical team approach. This study as well as others (Abel, 1990; Hannigan *et al*., 1992) have demonstrated that the current gestalt approach to diagnosis can often lead to diagnoses of FAS made solely on exposure, made in the absence of CNS dysfunction or made when only a single facial anomaly is present. The 4-Digit Code prevents this from occurring. Outcomes and exposures are reported independently so as not to imply that an *individual's* disabilities and/or anomalies are confirmed to be caused by their prenatal alcohol exposure. The 4-Digit Code serves as a standardized, descriptive language that will allow clinicians and researchers to clearly and objectively communicate the exposures and outcomes of their patients. Although the FAS DPN has gone one step further and clinically categorized and labeled the codes, use of the 4-Digit code is independent of this step, much like measuring and reporting birth weight in grams and centiles is independent of defining the cut-off for 'low birth weight'. Failure to reach consensus on the categorization and labeling of the codes need not prevent the use of the 4-Digit Codes. The 4-Digit diagnostic method is fully comprehensive. It can be used to diagnose individuals of all ages and races who present across the full spectrum of exposure and outcomes. This is achieved by directing the clinician to age-, gender- and race - adjusted anthropometric and psychometric measures when available and appropriate. The availability and reliability of outcome and exposure information varies across patients. The derivation of the 4-Digit Code addresses this reality by encoding both the presence and absence of outcome and exposure information. This method can be taught to a wide array of health care and social service providers, thus greatly expanding the availability of diagnostic services. Multidisciplinary clinical teams from six States in the U.S. and three Canadian Provinces have been trained to use the 4-Digit Code to date.

Although the 4-Digit diagnostic method was developed for prospective use in a fully staffed, multidisciplinary clinic, it can also be used in active and passive screening and surveillance efforts. Surveillance generally uses methods distinguished by their practicality, uniformity, and frequently their rapidity, rather

than by complete accuracy (Last, 1988). A key feature of the 4-Digit Diagnostic Code is that it not only documents exposure and outcome, but also documents how much data was available (or not available) to support the diagnostic outcome. The standardized FAS Diagnostic Evaluation Form served as an efficient tool for conducting the retrospective chart review on the 736 patients whose gestalt diagnoses were upgraded to 4-Digit Diagnostic Codes. The method provides an efficient and reproducible method for conducting retrospective chart reviews, a process that is the very essence of passive surveillance. The computerized facial analysis component of the 4-Digit Code also serves as an efficient and highly effective photographic method for screening for FAS (Astley *et al*., 1999). This method is currently being used to screen all children entering foster care in one county in WA State.

Meaningful progress in the areas of screening, diagnosis, intervention, surveillance and primary prevention all hinge on development of an accurate, precise, valid and efficient method for identification of individuals damaged by prenatal alcohol exposure. The 4-Digit Diagnostic Code was developed to achieve that goal in Washington State.

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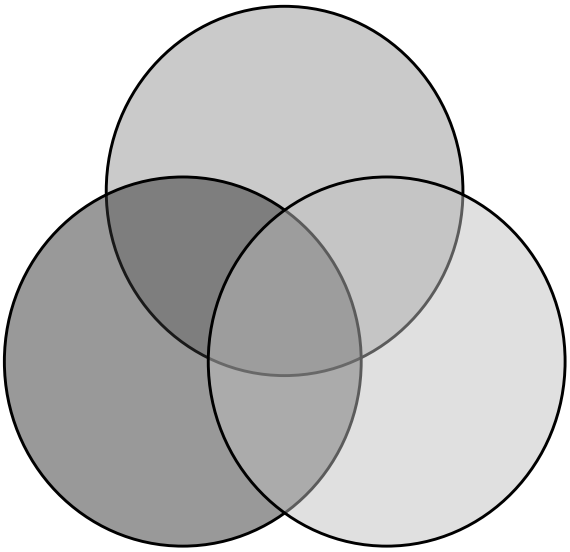

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John B. Chavez FAS Fund

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Preface

What's New in this Third Edition?

The first and second editions of the Diagnostic Guide were printed in 1997 and 1999 (Astley and Clarren, 1997, 1999). The key updates in this third edition are presented below. These updates are based on our use of the 4-Digit Code for the past seven years on over 2,000 patients, advancements in medical research, U.S. and Canadian efforts to establish National Diagnostic Guidelines, and feedback from over 70 clinical teams trained to use the 4-Digit Diagnostic Code. We will continue to make modifications that enhance accuracy, improve clarity, and increase ease of use. We hope you will find this comprehensive approach to the diagnosis of individuals with prenatal alcohol exposure helpful and broadly applicable.

Key updates in this 3rd edition include:

1. Re-Classification of Nineteen 4-Digit Codes across Seven Diagnostic Categories. Based on current efforts in the U.S. and Canada to establish National Diagnostic Guidelines, and our own experience using the 4-Digit Code, we have reclassified 19 of the 246 4-Digit Codes. Most of these reclassifications reflect the widespread consensus to relax the growth criteria. A detailed presentation of which codes were reclassified, why they were reclassified, and the impact the reclassification has on the prevalence of each diagnostic category can be found on the FAS DPN website (http://depts.washington.edu/fasdpn).
2. Modification of the growth deficiency case-definitions to harmonize with the U.S. and Canadian Diagnostic case-definitions for growth deficiency. This modification allows one to document and differentiate growth deficiency at both the 3rd and 10th percentiles.
3. Updated FASD Diagnostic Form with a new Functional Domains page. The FASD Diagnostic Form has been updated to provide a more comprehensive format. An additional page has been added to allow one to document "Domains of Brain Dysfunction". Documentation of impaired domains (e.g., cognition, memory, executive function, etc.) is a key component of the Canadian and U.S. National Diagnostic Guidelines and has always been required to derive/support a CNS Rank 3 classification when using the 4-Digit Code.
4. Updated Growth Charts. The most recent 2000 CDC growth charts are included with reference to their website for computerized charting of growth.
5. New Caucasian and African American Lip-Philtrum Guides, 2004. A new Caucasian Lip-Philtrum Guide was printed that uses higher-resolution, higher quality photographs. The magnitude of lip thinness and philtrum smoothness remain unchanged from the 1999 Caucasian Lip-Philtrum Guide. A new African American Lip-Philtrum Guide has also been created. The cut-off values for each of the five ranks in the African American Guide were set to be comparable to the percentile cutoffs used in the Caucasian Lip-Philtrum Guide. Both Guides require a Rank 4 or 5 lip and philtrum to meet the criteria for the FAS facial phenotype. The 2004 modified growth table is printed on the backside of each Lip-Philtrum Guide.

I. Introduction

A. What are Fetal Alcohol Syndrome (FAS) and Fetal Alcohol Spectrum Disorders (FASD)

FAS is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. The definition of the FAS has changed little since the 1970's when the condition was first described and refined (Jones and Smith, 1973; Rosett, 1980; Clarren and Smith, 1978; Sokol and Clarren, 1989; Stratton *et al*., 1996). The condition has been broadly characterized by prenatal and/or postnatal growth deficiency, a unique cluster of minor facial anomalies, and central nervous system (CNS) abnormalities. FAS is the leading known cause of mental retardation/developmental disabilities in the Western World (Abel & Sokol, 1987) and is entirely preventable. The prevalence of FAS is estimated to be 1 to 3 per 1,000 live births (Stratton et al., 1996) in the general population, but has been documented to be as high as 10 to 15 per 1,000 in some high-risk populations (Astley et al., 2002).

The physical, cognitive, and behavioral deficits observed among individuals with prenatal alcohol exposure are not dichotomous, that is either normal or clearly abnormal. Rather, the outcomes, and the prenatal alcohol exposure, all range along separate continua from normal to clearly abnormal and distinctive. This full range of outcomes observed among individuals with prenatal alcohol exposure has come to be called Fetal Alcohol Spectrum Disorders (FASD). The term FASD is not intended for use as a clinical diagnosis. A patient would not receive a diagnosis of FASD, for the term is too broadly defined to be of clinical value. FAS, on the other hand, is a clinical diagnosis and is one of several alcohol-related diagnoses that fall under the umbrella of FASD.

Although reference to the harmful effects of prenatal alcohol exposure on infant outcome dates back to the biblical literature, it was not until 1968 when the first reference was published in the medical literature by Lemoine and colleagues from France (Lemoine et al., 1968). Ulleland and colleagues from the United States published similar research findings in 1970 and 1972 (Ulleland et al., 1970; Ulleland, 1972). Using today's terminology, one could say Lemoine and Ulleland were the first to describe FASD in the medical literature. In 1973, Jones and Smith coined the term FAS (Jones & Smith, 1973) to describe a subset of alcohol-exposed children, obtained from Dr. Ulleland's study and their own clinical records, who shared a common pattern of malformation (Jones et al., 1973).

B. The Diagnostic Challenge

FASD can present a daunting, but not insurmountable challenge for diagnosis. Individuals with prenatal alcohol exposure present with a wide range of outcomes, most of which are not specific to prenatal alcohol exposure and often manifest differently across the lifespan. Professionals from multiple disciplines (medicine, psychology, speech-language pathology, occupational therapy, etc.) are needed to accurately assess and interpret the broad array of outcomes that define the diagnoses. The pattern and severity of outcome is dependent on the timing, frequency, and quantity of alcohol exposure (which is rarely known with any level of accuracy), and is frequently confounded by other adverse prenatal and postnatal exposures and events.

In the absence of accurate, precise, and unbiased methods for measuring and recording the severity of exposures and outcomes in individual patients, diagnoses have varied widely from clinic to clinic

(Aase, 1994; Astley & Clarren 2000; Chavez et al., 1988; Stratton et al., 1996). From a clinical perspective, diagnostic misclassification leads to inappropriate patient care, increased risk for secondary disabilities (Streissguth & Kanton, 1997) and missed opportunities for primary prevention. From a public health perspective, diagnostic misclassification leads to inaccurate estimates of incidence and prevalence (Stratton et al., 1996). Inaccurate estimates thwart efforts to allocate sufficient social, educational, and health care services to this high-risk population, and preclude accurate assessment of primary prevention intervention efforts. From a clinical research perspective, diagnostic misclassification reduces the power to identify clinically meaningful contrasts between FAS and control groups (Astley & Clarren, 2001). Non-standardized diagnostic methods prevent valid comparisons between studies.

The 4-Digit Diagnostic Code was originally created in 1997 to address the following limitations in the conventional gestalt approach to diagnosing individuals with prenatal alcohol exposure.

1. *There have been no standardized operational definitions for FAS or for any of the other diagnoses that fall under the umbrella of FASD. Rather, there have been diagnostic guidelines that physicians have been encouraged to follow, but the guidelines have not been sufficiently specific to assure diagnostic accuracy or precision.*

   For example, according to the diagnostic guidelines published by Sokol and Clarren (1989), which were a minor modification of the 1980 definition of FAS by the Fetal Alcohol Study Group of the Research Society for Alcoholism (Rosett, 1980), which, in turn, were derived from the work of Clarren and Smith (1978): "The diagnosis of FAS can only be made when the patient has signs of abnormality in each of the three categories: 1) Prenatal and/or postnatal growth retardation [weight and/or length below the 10^{th} percentile when corrected for gestational age], 2) central nervous system involvement (including neurological abnormality, developmental delay, behavioral dysfunction or deficit, intellectual impairment, and/or structural abnormalities, such as microcephaly [head circumference below the 3^{rd} percentile or brain malformations found on imaging studies or autopsy] and 3) a characteristic face, currently qualitatively described as including short palpebral fissures, an elongated midface, a long and flattened philtrum, thin upper lip, and flattened maxilla."

   The 1996 guidelines for the diagnosis of FAS proposed by the Institute of Medicine (Stratton et al., 1996) took a similar approach. The diagnosis of FAS can be made when the patient presents with: "1) Evidence of growth retardation, as in at least one of the following: a) low birth weight for gestational age; b) decelerating weight over time not due to nutrition; or c) disproportional low weight to height; 2) Evidence of a characteristic pattern of facial anomalies that includes features such as short palpebral fissures and abnormalities in the premaxillary zone (e.g., flat upper lip, flattened philtrum, and flat midface); and 3) Evidence of CNS neurodevelopmental abnormalities, as in at least one of the following: a) decreased cranial size at birth; b) structural brain abnormalities (e.g., microcephaly, partial or complete agenesis of the corpus callosum, cerebellar hypoplasia);c) neurological hard or soft signs (as age appropriate), such as impaired fine motor skills, neurosensory hearing loss, poor tandem gait, poor eye-hand coordination."

   Although these descriptions do provide guidance, they are not sufficiently specific to assure diagnostic accuracy and precision. They reflect a more "gestalt" approach to diagnosis. The guidelines for CNS abnormalities do not address how many areas of deficit must be present, how

severe the deficits must be, or what level of documentation must exist to substantiate the presence of the deficit. The guidelines for the facial phenotype are equally nonspecific. How many facial features must be present, how severe must the features be, and what scale of measurement should be used to judge the severity? One need only read the clinical literature or review medical records, birth certificates, birth defect registries or ICD-9 codes to see how variably these criteria are interpreted, applied and reported (CDC, 1995, 1995a; Cordero et al., 1994; Ernhart et al., 1995; Stratton et al., 1996).

New U. S. diagnostic guidelines for FAS (Bertrand et al., 2004) and Canadian diagnostic guidelines for FASD (Chudley et al., 2004) offer more standardized, case-defined criteria than those published in previous guidelines (Sokol and Clarren, 1989, Stratton et al., 1996). Both are slated for release in 2004.

2. *There has been a lack of objective, quantitative scales to measure and report the magnitude of expression of key diagnostic features*

   For example, although a thin upper lip and smooth philtrum are key diagnostic features (Astley & Clarren, 1996; Clarren & Smith, 1978; Jones & Smith, 1973; Smith, 1979; Stratton et al., 1996), quantitative measurement scales were never used to measure thinness or smoothness, and guidelines had never been established for how thin or smooth the features must be. Objective quantitative scales not only improve accuracy and precision, but also establish a common numeric language for communicating outcomes in medical records and in the medical literature.

3. *The term fetal alcohol effects (FAE) was broadly used and poorly defined.*

   The term 'suspected fetal alcohol effects' was first introduced into the medical literature in 1978 and was defined as 'less complete partial expressions' of FAS in individuals with prenatal alcohol exposure (Clarren & Smith, 1978). Based on this definition, an individual whose mother drank a few glasses of wine intermittently throughout pregnancy and presented with attention deficit hyperactivity disorder would meet the criteria for FAE. So would an individual whose mother drank a fifth of vodka daily throughout pregnancy and presented with microcephaly, severe mental retardation, growth deficiency and no facial anomalies. The broad use of this term and the reluctance to abandon it points to the clear need to develop diagnostic terms for individuals with prenatal alcohol exposure who present with physical anomalies and/or cognitive/behavioral disabilities, but do not meet the criteria for FAS. New diagnostic terms that more finely differentiate the variable exposures and outcomes of individual patients, without implying alcohol as the sole causal agent, are needed.

4. *Clinical terms like FAE* (Aase et al., 1995), *alcohol-related birth defects (ARBD) (Stratton et al., 1996) and alcohol-related neurodevelopmental disorder (ARND) (Stratton et al., 1996) imply a causal link between alcohol exposure and outcome in a given individual that, to date, cannot be medically confirmed. Leading dysmorphologists in the field of FAS diagnosis have formally requested that the term FAE no longer be used for this reason (Aase et al., 1995; Sokol & Clarren, 1989).*

   With the likely exception of the full facial phenotype, no other physical anomalies or cognitive/behavioral disabilities observed in an individual with prenatal alcohol exposure are necessarily specific to (caused only by) their prenatal alcohol exposure (Stratton et al., 1996). Features

such as microcephaly, neurological abnormalities, attention deficit, mental retardation, and growth deficiency frequently occur in individuals with prenatal alcohol exposure, and frequently occur in individuals with no prenatal alcohol exposure. The diagnostic terms ARBD and ARND introduce the same limitation as does FAE, namely, implying alcohol exposure caused the birth defect or neurobehavioral disorder in an individual patient. The 4-Digit Code avoids this problem by using a nomenclature that reports the patient was *exposed* to prenatal alcohol rather than reporting the patient's outcomes are *alcohol effects* or *alcohol-related outcomes*. The 4-Digit Code also requires that all other adverse prenatal and postnatal exposures and events be documented for they too serve as important risk factors that must be taken into consideration when deriving a diagnosis and intervention plan.

5. *Too often diagnoses depicting FASD are reported in the medical records and medical literature with no documentation of the method used to derive the diagnosis and little or no documentation of the data used to support the diagnosis.*

   Failure to report this information can limit the patient's ability to qualify for and receive appropriate intervention services from subsequent health care, social service, and educational providers. For example, simply reporting that an individual has FAS does little to convey the individual's strengths and disabilities. Some individuals with FAS have low IQs, some have normal IQs, some have attention deficits, some do not, some have problems with memory, while others have language deficits. From a public health perspective, failure to report these data also prevents surveillance efforts from accurately tracking the prevalence of FASD diagnoses in the population. The supportive data are needed to validate the diagnoses. Accurate surveillance is vital for setting public health policy and assessing the effectiveness of primary prevention efforts. The 4-Digit Code requires that data be collected not just to support the diagnosis, but to derive the diagnosis. The 4-Digit Code provides a comprehensive FASD Diagnostic Form for recording all supportive data and provides a numeric classification scheme that is readily incorporated into clinical, research, and surveillance databases.

C. Meeting the Diagnostic Challenge

Each of the above limitations has been largely overcome with the development of the "*4-Digit Diagnostic Code*". The four digits reflect the magnitude of expression of four key diagnostic features of FASD in the following order: (1) growth deficiency, (2) the FAS facial phenotype, (3) CNS abnormalities, and (4) prenatal alcohol exposure. The magnitude of expression of each feature is ranked independently on a 4-point Likert scale with 1 reflecting complete absence of the FAS feature and 4 reflecting a strong "classic" presence of the FAS feature. Thus, the 4-Digit Code 4444 reflects the most severe expression of FAS (significant growth deficiency, all three FAS facial features, structural/neurological evidence of CNS damage, and confirmed prenatal exposure to high levels of alcohol). At the opposite end of the scale is the 4-Digit Code 1111 reflecting normal growth, none of the three FAS facial features, no evidence of CNS abnormalities, and confirmed absence of prenatal alcohol exposure. Every combination of 4-Digit Code has been observed in the Washington State FAS Diagnostic & Prevention Network.

This diagnostic method was developed through the combined expertise of the University of Washington FAS Diagnostic and Prevention Network (FAS DPN) interdisciplinary clinical team

(Clarren & Astley, 1997; Clarren et al., 2000) and the comprehensive records of over 2,000 patients (birth to 53 years of age) diagnosed through the FAS DPN.

D. Benefits of the 4-Digit Diagnostic Code

The 4-Digit Diagnostic Code:

1. Greatly increases diagnostic precision and accuracy through the use of objective, quantitative measurement scales, image analysis software, and specific case definitions.
2. Diagnoses the full spectrum of outcomes (FASD) observed in individuals of all ages with prenatal alcohol exposure.
3. Offers an intuitively logical numeric approach to reporting outcomes and exposure that reflects the true diversity and continuum of disability associated with prenatal alcohol exposure.
4. Documents the presence of prenatal alcohol exposure without judging its causal role.
5. Documents all other prenatal and postnatal adverse exposures and events that can also impact outcome.
6. Provides a quantitative measurement and reporting system that can be used independent of diagnostic nomenclature.
7. Can be taught to a wide array of health care and social service providers, thus greatly expanding the availability of diagnostic services. (Appendix 1)

The 4-Digit Code currently serves as the cornerstone of a fully integrated and highly successful screening, diagnostic, prevention and surveillance program in Washington State (Astley et al., 2002; Astley, 2004).

While this document might at first appear overly complex and perhaps daunting, one will find that this diagnostic approach is logical and easy to use, and will greatly facilitate the proper description and classification of patients presenting with all possible combinations of outcomes and exposures.

E. Other Syndromes

The methods of diagnosing fetal alcohol syndrome arise from the larger fields of teratology and dysmorphology (clinical genetics). It is essential to remember that many birth defect syndromes share *isolated* features, but each is differentiated by a unique *constellation* of features. A few examples of conditions that share some, but not all, of the features of FAS include fetal hydantoin syndrome, maternal PKU fetal effects, and fetal valproate syndrome. Although this guide is "FASD-specific", this in no way should imply that the diagnostician need not consider alternate or co-existing syndromic, medical or psychiatric conditions at all times. A differential diagnosis is essential in making an accurate diagnosis.

II. FASD Diagnostic Form

The FASD Diagnostic Form guides the interdisciplinary clinical team in the collection, recording, and interpretation of all key information used to derive accurate and precise diagnoses across the full spectrum of outcomes. Comprehensive assessments lead to accurate diagnoses and informed intervention plans. Although space has been provided to record a full complement of data, we are not implying that all of these assessments must be conducted to derive a diagnosis. It is the responsibility of the clinical team to select the most appropriate assessment battery for each patient.

The form also serves as a centralized data repository for efficient generation of the final medical report and is designed to facilitate data entry into a database.

Where is the Information for the Diagnostic Form Obtained?

The information recorded in the FASD Diagnostic Form is obtained from four primary sources:

1. The New Patient Information Form completed by the caregivers prior to the diagnostic evaluation (Appendix 2).

2. Medical/psychological/educational assessments conducted prior to the diagnostic evaluation.

3. Assessments administered by the clinical team at the time of the diagnostic evaluation.

4. The caregiver/patient interview conducted at the time of the diagnostic evaluation

When is the Form Completed and by Who?

Diagnosis of fetal alcohol spectrum disorders by a multidisciplinary team of professionals (physician, psychologist, speech-language pathologist, occupation therapist, etc.) will result in the most accurate assessment and interpretation of the broad array of outcomes (growth deficiency, facial anomalies, and structural/neurological/functional CNS abnormalities) that define the diagnoses. The FASD Diagnostic Form is completed by the clinical team before and during the patient's clinic visit. Typically, the physician completes the sections pertaining to growth, structural and neurological measures of the CNS, facial features and other physical findings. The occupational therapist, psychologist, speech language pathologist, and/or other team members complete the sections pertaining to psychometric measures of CNS function. All team members participate in the derivation of the 4-Digit Code and intervention plan.

Diagnostic Form, Section II Diagnostic Guide for FASD

FASD Diagnostic Form

Medical #		Clinic		Clinic Date	
Patient's Name	First	MI	Last	Age (y)	Birth date

Name person(s) accompanying			
Relationship(s) to patient		Patient's Gender	M F

Patient's Race	
Form completed by:	
Diagnosis made by:	
Diagnosis	

4-Digit Diagnostic Code Grid

(See instructions in Diagnostic Guide for FASD)

Growth Deficiency	FAS Facial Features	CNS Damage		Growth	Face	CNS		Alcohol	Prenatal Alcohol
Significant	Severe	Definite	4					4	High risk
Moderate	Moderate	Probable	3					3	Some risk
Mild	Mild	Possible	2					2	Unknown
None	None	Unlikely	1					1	No risk

GROWTH

Prenatal Growth

	Gestational Age	Birth Length			Birth Weight		
Date	(wks)	(cm)	(inches)	(percentile)	(gm)	(lbs/oz)	(percentile)

Postnatal Growth

		Height					Weight		
Date	Age (yrs/months)	(cm)	(inches)	Unadjusted (percentile)	Mid-birthparent Adjustment (cm)	Parent-Adjusted (percentile)	(kg)	(lbs)	(percentile)

Birth Parent's Heights

Birth Mother Height		Birth Father Height		Mid-Parent Height
cm	inches	cm	inches	cm

ABC-Score for Growth Deficiency

See instructions in the "Diagnostic Guide for FASD" for deriving the ABC-score for growth and translating it into a 4-Digit Diagnostic Code

	Circle the ABC Scores for: Height	Weight
≤ 3rd percentile = **C**	C	C
>3rd and ≤ 10th percentile = **B**	B	B
> 10th percentile = **A**	A	A

This ABC Score reflects the patient's growth between _____ years and _____ years of age.

FACIAL FEATURES (and other physical findings)

CURRENT PHENOTYPE: (Age _____ yrs/months)

Direct Measures

	True estimate (mm)	z-score	Normal Chart Used
Left PFL			
Right PFL			
Mean PFL			
Inner Canthal Distance			

	5-Point Rank	Lip-Philtrum Guide Used
Philtrum		
Upper Lip		

Clinic Photograph

Frontal digital photo filename	Internal measure of scale (dot on forehead)		
	True dot size	Units (mm, cm, inches)	Dot size in photo

	Length in photo (pixel or mm)	True estimate (mm)	z-score	Normal Chart Used
Left PFL				
Right PFL				
Mean PFL				
Inner Canthal Distance				

Photo filename		5-Point Rank	Lip-Philtrum Guide Used	
	Philtrum			Upper Lip Circularity
	Upper Lip			

PAST PHENOTYPE (Age _____ yrs/months) (Date _____/_____/_____)

Source of Information	Internal measure of scale (dot on forehead)		
	True dot size	Units (mm, cm, inches)	Dot size in photo (pixels)
Photo:			
Text Record:			

	Length in photo (pixel or mm)	True estimate (mm)	z-score	Normal Chart Used
Left PFL				
Right PFL				
Mean PFL				
Inner Canthal Distance				

Photo filename		5-Point Rank	Lip-Philtrum Guide Used	
	Philtrum			Upper Lip Circularity
	Upper Lip			

FACIAL ABC-SCORE *See instructions in the "Diagnostic Guide for FASD" for deriving the ABC Score and 4-Digit Code*

5-Point Likert Rank for Philtrum & Lip	Z-score for Palpebral Fissure Length	*Circle the ABC Scores for:* Palpebral Fissure	Philtrum	Upper Lip
4 or 5	≤ -2 SD	C	C	C
3	>-2 SD and ≤ -1 SD	B	B	B
1 or 2	> -1 SD	A	A	A
Source of Data for each Facial Feature →				

OTHER PHYSICAL FINDINGS / SYNDROMES / MEDICAL CONDITIONS

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CENTRAL NERVOUS SYSTEM (CNS)

Severity Score: Severity of Delay/Impairment (Displayed along left margin)
Circle: **0** = Unknown, Not Assessed **1** = Within Normal Limits **2** = Mild to Moderate **3** = Significant

Severity **STRUCTURAL**

0 1 2 3	OFC	cm	%tile	age (yrs/mos)	cm	%tile	age (yrs/mos)	cm	%tile	age (yrs/mos)

0 1 2 3 Structural anomalies seen on brain imaging _____

0 1 2 3 Other: _____

NEUROLOGICAL

0 1 2 3 Seizures: type:_____ meds._____ Age at onset _____(yrs/mos)

0 1 2 3 Other neurological signs: _____

_____

FUNCTIONAL/Standardized Measures *Document most recent, valid test scores.*

0 1 2 3 **Cognition** (e.g., WISC-III, WAIS, DAS, Stanford-Binet, etc.)

Test Name	*Age (yr/mos) or Date*	*FSIQ*	*PIQ*	*VIQ*	*Verb. Comp*	*Percept Org.*	*Free. Distr.*	*Process. Speed*

Info	*Simil.*	*Arith.*	*Voc.*	*Comp*	*Digit.*	*Pict. C.*	*Pict. A.*	*Block*	*Obj.*	*Coding*	*Mazes*	*Symbol*

Other Test/Subtest Names	*Score*	*Type of Score*	*Age (yr/mos) or Date*	*Other Test/Subtest Names*	*Score*	*Type of Score*	*Age (yr/mos) or Date*

0 1 2 3 **Academic Achievement** (e.g., WIAT, Woodcock Johnson, WRAT, etc)

Test/Subtest Name	*Score*	*Type of Score*	*Age (yr/mos) or Date*	*Test/Subtest Name*	*Score*	*Type of Score*	*Age (yr/mos) or Date*

0 1 2 3 **Adaptive Behavior / Social Skills** (e.g., VABS, BASC, Adaptive Behavior Assessment System, etc)

Test/Subtest Name	*Score*	*Type of Score*	*Age (yr/mos) or Date*	*Test/Subtest Name*	*Score*	*Type of Score*	*Age (yr/mos) or Date*

CNS (Continued)

Severity Score: Severity of Delay/Impairment (Displayed along left margin)
Circle: **0** = Unknown, Not Assessed **1** = Within Normal Limits **2** = Mild to Moderate **3** = Significant

Severity

0 1 2 3 **Neuropsychological** (e.g., CVLT, D-KEFS, WRAML, CMS, Rey Complex Figure Test, WCST, NEPSY, etc)

Test/Subtest Name	*Score*	*Type of Score*	*Age (yr/mos) or Date*	*Test/Subtest Name*	*Score*	*Type of Score*	*Age (yr/mos) or Date*

0 1 2 3 **Motor / Sensory Integration** (e.g., PDMS, SSP, QNST, VMI, Brunuinks-Oseretsky Scales of Motor Dev, etc.)

Test/Subtest Name	*Score*	*Type of Score*	*Age (yr/mos) or Date*	*Test/Subtest Name*	*Score*	*Type of Score*	*Age (yr/mos) or Date*

0 1 2 3 **Language/Social Communication** (e.g., TOLD, PLS-3, Narrative production, Mental state reasoning, etc)

Test/Subtest Name	*Score*	*Type of Score*	*Age (yr/mos) or Date*	*Test/Subtest Name*	*Score*	*Type of Score*	*Age (yr/mos) or Date*

CNS (Continued)

Severity Score: Severity of Delay/Impairment (Displayed along left margin)
Circle: **0** = Unknown, Not Assessed **1** = Within Normal Limits **2** = Mild to Moderate **3** = Significant

Severity

0 1 2 3 **Mental Health/Psychiatric Conditions:** (e.g., ODD, Generalized Anx. Disorder, Maj. Depression, etc)

Disorder	*Age (yr/mos) or Date Diagnosed*	*Disorder*	*Age (yr/mos) or Date Diagnosed*	*Disorder*	*Age (yr/mos) or Date Diagnosed*

Medication. √ if Currently Taking	*Response (+, -, none)*	*Medication. √ if Currently Taking*	*Response (+, -, none)*	*Medication. √ if Currently Taking*	*Response (+, -, none)*

0 1 2 3 **Behavior/Attention/Activity Level** (e.g., CBCL, Conners Rating Scale, Continuous Perform. Test, IVA, etc.)

Test/Subtest Name	*Score*	*Type of Score*	*Age (yr/mos) or Date*	*Test/Subtest Name*	*Score*	*Type of Score*	*Age (yr/mos) or Date*

0 1 2 3 **Development** (e.g., Bayley Scales of Infant Dev., Battelle Dev. Invent., Miller Assessment of Preschoolers, etc.)

Test/Subtest Name	*Score*	*Type of Score*	*Age (yr/mos) or Date*	*Test/Subtest Name*	*Score*	*Type of Score*	*Age (yr/mos) or Date*

CNS (Continued)

FUNCTIONAL / Non-Standardized Observational Measures

Severity Score: Severity of Delay/Impairment (Displayed along left margin)
Circle: **0** = Unknown, Not Assessed, Too Young **1** = Within Normal Limits **2** = Mild to Moderate **3** = Significant

Severity

Caregiver Interview

Planning / Temporal Skills

0 1 2 3 Needs considerable help organizing daily tasks_____
0 1 2 3 Can not organize time _____
0 1 2 3 Does not understand concept of time_____
0 1 2 3 Difficulty in carrying out multi-step tasks _____
0 1 2 3 Other _____

Behavioral Regulation/ Sensory Motor Integration

0 1 2 3 Poor management of anger / tantrums _____
0 1 2 3 Mood swings _____
0 1 2 3 Impulsive _____
0 1 2 3 Compulsive _____
0 1 2 3 Perseverative _____
0 1 2 3 Inattentive _____
0 1 2 3 Inappropriately [high or low] activity level _____
0 1 2 3 Lying/stealing _____
0 1 2 3 Unusual [high or low] reactivity to [sound touch light] _____
0 1 2 3 Other _____

Abstract Thinking / Judgment

0 1 2 3 Poor judgment _____
0 1 2 3 Cannot be left alone _____
0 1 2 3 Concrete, unable to think abstractly_____
0 1 2 3 Other _____

Memory / Learning / Information Processing

0 1 2 3 Poor memory, inconsistent retrieval of learned information _____
0 1 2 3 Slow to learn new skills_____
0 1 2 3 Does not seem to learn from past experiences_____
0 1 2 3 Problems recognizing consequences of actions_____
0 1 2 3 Problems with information processing speed and accuracy_____
0 1 2 3 Other _____

Spatial Skills and Spatial Memory

0 1 2 3 Gets lost easily, has difficulty navigating from point A to point B _____
0 1 2 3 Other _____

Social Skills and Adaptive Behavior

0 1 2 3 Behaves at a level notably younger than chronological age _____
0 1 2 3 Poor social/adaptive skills _____
0 1 2 3 Other _____

Motor/Oral Motor Control

0 1 2 3 Poor/delayed motor skills_____
0 1 2 3 Poor balance_____
0 1 2 3 Other _____

CNS (Continued)

FUNCTIONAL DOMAINS

Examples include, but are not limited to Memory, Cognition, Language, Executive Function, and Attention.

Severity Score: Severity of Delay/Impairment (Displayed along left margin)
Circle: **0** = Unknown, Not Assessed **1** = Within Normal Limits **2** = Mild to Moderate **3** = Significant

Severity

0 1 2 3 Name of Domain: ____________________
Supportive Evidence: ____________________
____
____

0 1 2 3 Name of Domain: ____________________
Supportive Evidence: ____________________
____
____

0 1 2 3 Name of Domain: ____________________
Supportive Evidence: ____________________
____
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0 1 2 3 Name of Domain: ____________________
Supportive Evidence: ____________________
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0 1 2 3 Name of Domain: ____________________
Supportive Evidence: ____________________
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0 1 2 3 Name of Domain: ____________________
Supportive Evidence: ____________________
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0 1 2 3 Name of Domain: ____________________
Supportive Evidence: ____________________
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0 1 2 3 Name of Domain: ____________________
Supportive Evidence: ____________________
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0 1 2 3 Name of Domain: ____________________
Supportive Evidence: ____________________
____
____

0 1 2 3 Name of Domain: ____________________
Supportive Evidence: ____________________
____
____

See the "Diagnostic Guide for FASD" for instructions on deriving the 4-Digit Diagnostic Code for CNS

MATERNAL ALCOHOL USE

Alcohol Consumption of the Birth Mother

Before Pregnancy	**average number of drinks** per drinking occasion:					
	maximum number of drinks per occasion:					
	average number of **drinking days per week**:					
	Type(s) of alcohol	wine	beer	liquor	unknown	Other (specify)

During Pregnancy	**average number of drinks** per drinking occasion:					
	maximum number of drinks per occasion:					
	average number of **drinking days per week**:					
	Type(s) of alcohol	wine	beer	liquor	unknown	Other (specify)

Trimester(s) in which alcohol was consumed	1st	2nd	3rd	unknown	none
Was the birth mother ever reported to have a **problem** with alcohol?	yes	suspected	no	unknown	
Was the birth mother ever **diagnosed** with alcoholism?	yes	suspected	no	unknown	
Did the birth mother ever **receive treatment** for alcohol addiction?	yes	suspected	no	unknown	
Was alcohol use during this pregnancy **positively confirmed**?	yes	no			
If yes, **source** of confirmation:					
Reported use of alcohol during this pregnancy is:	Reliable	Somewhat reliable		Unk. reliability	
Other information about alcohol use **during** this pregnancy					

4-DIGIT RANK for Alcohol Exposure

4-Digit Diagnostic Rank	Prenatal Alcohol Exposure Category	Description
4	High Risk	● Alcohol use during pregnancy is CONFIRMED. *and* ● Exposure pattern is consistent with the medical literature placing the fetus at "high risk" (generally high peak blood alcohol concentrations delivered at least weekly in early pregnancy).
3	Some Risk	● Alcohol use during pregnancy is CONFIRMED. *and* ● Level of alcohol use is less than in Rank (4) or level is unknown.
2	Unknown Risk	● Alcohol use during pregnancy is UNKNOWN.
1	No Risk	● Alcohol use during pregnancy is CONFIRMED to be completely ABSENT from conception to birth.

Circle the 4-Digit Diagnostic Rank in the table above that best reflects the patient's Prenatal Alcohol Exposure

OTHER PRENATAL AND POSTNATAL EXPOSURES / EVENTS

PRENATAL

High risk	Some risk	Unknown risk	No risk
4	3	2	1

See the "Diagnostic Guide for FASD" for instructions on deriving the rank for Prenatal Exposures/Events

Prenatal

1. Parity ____, Gravity ____ of this birth. Birth order if child is the result of a multiple birth pregnancy: _____ of _____
2. Prenatal care: ____ Yes, (If yes, when did it start?_____), ___ No, ___ Unknown
3. Complications (specify) _____

Genetics

1. Parental learning difficulties (e.g. Special Ed., ADD, MR, did not complete high school, etc.*)*

   Mother _____ Yes _____ Suspected _____ No _____ Unknown

   Father _____ Yes _____ Suspected _____ No _____ Unknown

   If yes, specify Maternal _____

   Paternal _____
2. Other conditions of heritability or malformation that may be relevant to this case. *(specify)*

   _____

Prenatal Exposure to Other Substances (e.g., medications, tobacco, illicit drugs, other teratogens, etc.)

_____

_____

POSTNATAL

High risk	Some risk	Unknown risk	No risk
4	3	2	1

See the "Diagnostic Guide for FASD" for instructions on deriving the rank for Postnatal Exposures/Events

Perinatal Difficulties

_____

_____

Issues of Nurture

1. Abuse: Physical _____ Sexual _____
2. Number of home placements _____
3. Other (e.g., neglect, adverse home environment, significant traumas, etc.*)* _____

   _____

   _____

   _____

Other Issues That Could Explain CNS Abnormalities (e.g., head injury, substance abuse by patient, etc.)

_____

_____

FAS Diagnostic and Prevention Network
Preliminary Summary and Recommendations

A final comprehensive medical summary will be mailed to you.

Patient's Name: _____ Clinic: _____

Birth Date: ____ / ____ / ____ Clinic Date: ___ / ___ / ___ Clinic phone: _____

Diagnostic Outcome: _____

Result(s) of assessment(s) performed in Clinic (if applicable):

FAS Diagnostic and Prevention Network
Preliminary Summary and Recommendations

Patient Name: _____ Birth Date: _____ / _____ / _____

Recommendations for Follow-Up

A. Medical Issues

_____

_____

_____

_____

_____

_____

B. Developmental, Educational, Vocational, Mental Health, and Family Issues

_____

_____

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III. Instructions for Deriving the 4-Digit Code

A. The 4-Digit Diagnostic Code

What are the 4 Digits?

The four digits reflect the magnitude of expression of the four key diagnostic features of FASD in the following order: (1) growth deficiency, (2) the FAS facial phenotype, (3) CNS abnormalities, and (4) prenatal alcohol exposure. The 4-Digit Diagnostic Code is generated at the completion of the diagnostic evaluation using information recorded on the FASD Diagnostic Form. The code is derived following the directions in Sections III. B. 1 through B. 4.

4-Digit Diagnostic Code Grid

				3	4	4		4		
Severe	Severe	Definite	(4)		X	X		X	(4)	High risk
Moderate	Moderate	Probable	(3)	X					(3)	Some risk
Mild	Mild	Possible	(2)						(2)	Unknown
None	None	Unlikely	(1)						(1)	No Risk
Growth Deficiency	**FAS Facial Features**	**CNS Damage**		Growth	Face	CNS		Alcohol		**Prenatal Alcohol**

The 4-Digit Diagnostic Code 3444 inserted in the grid is one of twelve 4-Digit Codes that meet the diagnostic criteria for FAS.

How are the 4 Digits Ranked?

The magnitude of expression of each feature is ranked independently on a 4-point Likert scale with 1 reflecting complete absence of the FAS feature and 4 reflecting a strong "classic" presence of the FAS feature. Specific guidelines for ranking the magnitude of each of the FAS features are presented in Section III.B.

How Many 4-Digit Diagnostic Codes are There?

There are 256 possible 4-Digit Diagnostic Codes ranging from 1111 to 4444. The 256 codes and their corresponding clinical names are listed in numerical order in Section VI.

How Many Different Clinical Diagnostic Categories are There?

Each 4-Digit Diagnostic Code falls into one of 22 unique Clinical Diagnostic Categories (labeled A through V). A list of the 22 Diagnostic Categories is presented in Section IV. A list of the 4-Digit Diagnostic Codes, which fall within each Clinical Diagnostic Category, is presented in Section V.

What are the Names of the Clinical Diagnostic Categories?

The following terms are used in varying combinations to name the 22 diagnostic categories. They include:

- **Sentinel Physical findings:**
  The term "S*entinel Physical Findings*" is used in this diagnostic system when the patient presents with growth deficiency at the Rank 3 or 4 level and/or presents with the FAS facial phenotype at the Rank 3 or 4 level. The adjective *"sentinel"* refers to physical findings that are key diagnostic features of FAS. These include a unique cluster of minor facial anomalies (short palpebral fissures, thin upper lip, and a smooth philtrum) and growth deficiency. Other physical findings (major or minor anomalies) may be detected instead of or in addition to these sentinel findings that may suggest alternate or additional conditions. There are places on the Diagnostic Form to record and interpret other physical findings.

- **Static Encephalopathy:**
  The term *"encephalopathy"* refers to "any significant abnormal condition of the structure or function of brain tissues" (Anderson, 2002). The term *"static"* means that the abnormality in the brain is unchanging; neither progressing nor regressing. The term *"Static Encephalopathy"* is used in this diagnostic system when the patient presents with significant structural, neurological, and/or functional abnormalities that strongly support the presence of underlying CNS damage at the Rank 3 and/or Rank 4 levels. The term does not define or suggest any specific pattern of structural, neurological, or functional abnormality.

- **Neurobehavioral Disorder:**
  The term *"Neurobehavioral Disorder"* is used in this diagnostic system when the patient presents with cognitive/behavioral dysfunction at the Rank 2 level and no evidence of structural, neurological or functional abnormalities at the Rank 3 or Rank 4 levels.

- **Alcohol (Exposed, Not Exposed, Exposure Unknown):**
  These terms are used to reflect prenatal alcohol exposure and its potential risk to the unborn child. Alcohol exposure is reported <u>independently</u> of outcome(s) and does not imply that a causal association exists between the exposure and the outcome(s).

- **Fetal Alcohol Syndrome (alcohol exposed)**
  The term FAS is used to refer to patients who present with one of twelve 4-Digit Diagnostic Code combinations reflecting growth deficiency; the full FAS facial phenotype; significant structural, neurological, and/or functional CNS abnormalities; and confirmed prenatal alcohol exposure. These 12 Codes are presented in Section V.

- **Fetal Alcohol Syndrome (alcohol exposure unknown)**
  A diagnosis of FAS can be rendered when prenatal alcohol exposure is "unknown" but only when the outcomes (growth, face, and CNS) are at the severe end of the spectrum to maintain the specificity of these outcomes to prenatal alcohol exposure. (Astley et al., 2001) Six 4-Digit Codes fall under this category (Section V).

- **Partial Fetal Alcohol Syndrome (alcohol exposed):**
  This term is used for patients who present with static encephalopathy, most (but not all) of the growth and/or facial features of FAS, and have a confirmed history of prenatal alcohol exposure. Given the fact that variable presentation is the rule rather than the exception after teratogenic exposures, we felt it was appropriate to establish this diagnostic category. Twenty 4-Digit Codes fall under this category (Section V).

- **Fetal Alcohol Syndrome Phenocopy (no alcohol exposure):**
  This term is used for patients who meet the growth, face and CNS criteria for FAS, but have a confirmed absence of alcohol exposure during gestation. We have never seen such a case (or phenocopy), but we may some day.

The names assigned to each diagnostic category reflect the patient's clinical outcome and alcohol exposure. The names are listed in Sections IV and V. The first three categories (A through C) meet the criteria for a clinical diagnosis of FAS and are named as such. The fourth category (D) applies to the patient who presents with all of the features of FAS, but has a confirmed *absence* of prenatal alcohol exposure from conception to birth. This category is referred to as a FAS Phenocopy and has yet to be observed. The remaining 19 categories (E through V) do not meet the minimum criteria for FAS or partial FAS. These are subsequently named to reflect the Likert ranking of each digit in the 4-Digit Diagnostic Code. For example, a code of 3243 is the Diagnostic Category called "*Sentinel physical finding(s) / static encephalopathy (alcohol exposed)*".

Which Diagnostic Categories are Comparable to PFAE, ARND and ARBD?

Many 4-Digit Codes within Diagnostic Categories E through I would previously have been referred to as "possible fetal alcohol effects" (PFAE), "alcohol-related birth defects" (ARND) or "alcohol-related neurodevelopmental disorder" (ARBD). (Sokol & Clarren, 1989; Stratton et al., 1996) A report that translates which 4-Digit Codes meet the criteria for ARND and ARBD can be found on the FAS DPN website http://depts.washington.edu/fasdpn. Categories J through V are categories that describe a large number of patient groups who have never been adequately classified or described by previous FASD diagnostic guidelines.

Ultimately, establishing terms that are both clinically accurate, broadly applicable, and facilitate access to services remains a challenge. It is important to remember that the 4-Digit Code provides a numeric measurement and reporting system for exposures and outcomes that can be used independently of the proposed diagnostic nomenclature.

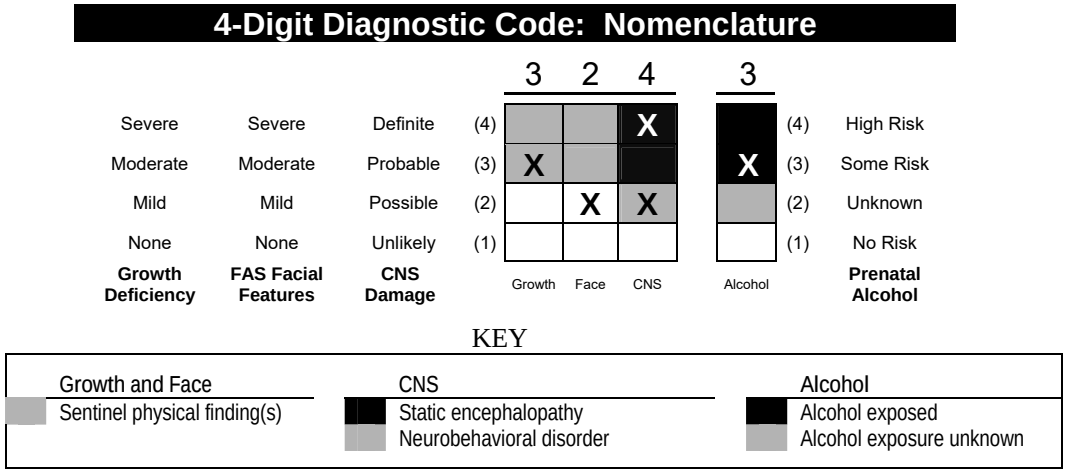
How are the Names of the Clinical Diagnostic Category Constructed?

- Growth deficiency and facial features are physical features. When either feature receives a rank of 3 or 4, *Sentinel physical finding(s)* is placed at the beginning of the name.

- When CNS receives only a Rank 2, the term *Neurobehavioral Disorder* is included in the name. When CNS receives a Rank 3 or 4, the term *Static Encephalopathy* is included in the name.

- When alcohol exposure receives a Rank 3 or 4, (*alcohol exposed*) is placed at the end of the name. When alcohol exposure receives a Rank 2, (*alcohol exposure unknown*) is placed at the end of the name.

- When the criteria for FAS or PFAS are met, those clinical terms are used in place of the more generic terms. For example the term FAS is used rather than *Sentinel physical finding(s / static encephalopathy (alcohol exposed).*



The 4-Digit Code 3243 would receive the clinical name *Sentinel physical finding(s) / static encephalopathy (alcohol exposed).* Note that the CNS received both Rank 4 and Rank 2. The higher Rank is used to derive the 4-Digit Code and construct the name. A code of 1222 would receive the clinical name *Neurobehavioral disorder (alcohol exposure unknown).*

How Do You Explain the Diagnosis to the Patient?

Generic summaries of each of the 22 Clinical Diagnostic Categories are presented in Section VII. These summaries can be used as the first page of the patient's final Medical Summary Note. Subsequent pages in the Medical Summary Note should document the findings and recommendations specific to the patient. We recommend the growth, face, CNS, and exposure data, used to generate the 4-Digit Code, be reported in the Medical Summary Note to provide essential information to subsequent medical professionals and facilitate records-based public health surveillance efforts.

III. Instructions for Deriving the 4-Digit Code

B.1. Ranking Growth

What Type of Growth Deficiency Are We Looking For?

We are looking for growth deficiency characteristic of a teratogenic insult, not characteristic of postnatal environmental factors such as nutritional deprivation or chronic or acute illness. We want to answer the question *'What is the patient's growth potential after controlling for parental height and postnatal environmental influences?'* Growth deficiency of teratogenic origin is likely to present as a relatively consistent impairment over a period of time (i.e., the patient's growth follows the normal curve, but is below genetic expectation for family background). In contrast, growth deficiency due to postnatal environmental influences is likely to present as periodic fluctuations in the curve. Separating the two growth patterns requires astute clinical judgment.

The method described below allows one to rank a patient's overall growth pattern on a single 4-point Likert scale with 1 equal to 'normal' and 4 equal to significantly deficient. Not all patients will have complete growth curves available, therefore, a guide is provided below for prioritizing the ranking of the patient's growth over a lifetime

How to Measure and Rank Growth: The 1st Digit of the 4-Digit Diagnostic Code

A. The height percentile should be age and gender adjusted. Because there is a significant genetic component in attained stature, adjustment for mid-parent stature is also recommended when both parents' heights are known. Himes et. al., (1985) provide charts for mid-parent adjustment of recumbent length (birth to 3 years) and stature (3 to 18 years) of US children relative to National Center for Health Statistics growth charts.

B. The weight percentile should be age and gender adjusted. Weight is not adjusted for height.

   CDC 2000 Growth Charts are provided in Section VIII. Other valid growth charts may be used. We recommend electronic computation of percentiles for increased accuracy. CDC offers a free software program called Epi Info that will compute percentiles and plot data on the CDC Growth Charts. This software can be obtained from the CDC website www.cdc.gov/epiinfo.

C. For ranking purposes, the growth record is separated into two parts:
   1. Prenatal growth (birth measures)
   2. Postnatal growth (all measures collected after birth)

   Select the part of the growth record with the greatest deficiency in the height percentile.

   If the prenatal height percentile is lower than all postnatal height percentiles, proceed to section D for instructions on how to rank prenatal growth.

If any of the postnatal height percentiles are lower than the prenatal height percentile, select the point or consecutive points in the growth record that reflect the lowest height percentiles that cannot be attributed to postnatal environmental influences such as nutritional deprivation or chronic illness. If the height deficiency is reflected in a series of points in the growth record, as opposed to a single point, rank the level of deficiency based on the percentile range where the majority of the points fall. Proceed to section D for instructions.

D. Rank the level of deficiency of the height and weight percentiles, for the part of the growth record with greatest deficiency in the height percentile by circling A, B, or C in the ABC-Score table at the bottom of page 1 of the FASD Diagnostic Form. This ABC-Score table is duplicated below as Table 1. The height and weight percentiles selected for ranking should be matched sets. For example, if the height at 10 years of age is selected for ranking, the corresponding weight percentile at 10 years of age should also be selected for ranking. One does not rank the height at one age and the weight at another age to generate an ABC-Score.

Table 1: Deriving the ABC-Score for Growth

	Circle the ABC-Scores for:	
Percentile Range	Height	Weight
$\leq 3^{rd}$	C	C
$>3^{rd}$ and $\leq 10^{th}$	B	B
$>10^{th}$	A	A

E. Next, refer to Table 2 to determine the *4-Digit Diagnostic Rank* of the Height-Weight ABC-Score recorded in Table 1. Transfer the resulting 4-Digit Diagnostic Rank for growth to the 4-Digit Diagnostic Code Grid at the top of page 1 of the FASD Diagnostic Form.

Table 2: Converting the Growth ABC-Score to a 4-Digit Diagnostic Rank for Growth

4-Digit Diagnostic Rank	Growth Deficiency Category	Height-Weight ABC-Score Combinations
4	Severe	CC
3	Moderate	CB, BC, CA, AC
2	Mild	BA, BB, AB
1	None	AA

Example for Scoring Growth Deficiency

Patient's Growth Record:

	Age (years)	Height Percentile	Weight Percentile
birth	0.0	8 %	1 %
	1.5	14 %	16 %
	5.0	12 %	15 %
	7.0	12 %	15 %
	15.5	15 %	15 %

Assume the clinical records rule-out any environmental influence on postnatal measures and mid-parental height is unknown.

Ranking:

- Priority would be placed on ranking the birth length and weight because the birth length percentile is lower than all postnatal height percentiles recorded.
- Birth length (8 %) would receive an **ABC-Score = B** (> 3rd and ≤ 10th percentile) (Table 1).
- Birth weight (1 %) would receive an **ABC-Score = C** (≤ 3rd percentile) (Table 1).
- The Height-Weight ABC-Score combination would be **BC** (Table 1).

Table 1: Deriving the ABC Score for Growth

	Circle the ABC-Scores for:	
Percentile Range	Height	Weight
≤ 3rd	C	**C**
>3rd and ≤ 10th	**B**	B
>10th	A	A

- The Height-Weight ABC-Score of **BC** reflects **Moderate** growth deficiency (Table 2)
- **Moderate** growth deficiency would receive a **Rank 3** in the 4-Digit Diagnostic Code (Table 2).

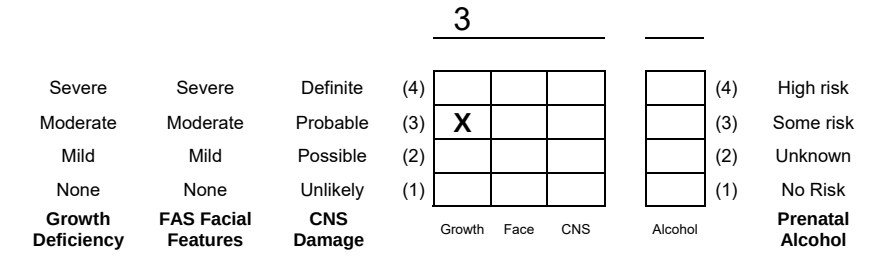
Table 2: Converting the Growth ABC-Score to a 4-Digit Diagnostic Rank for Growth

4-Digit Diagnostic Rank	Growth Deficiency Category	Height-Weight ABC-Score Combinations
4	Severe	CC
3	**Moderate**	CB, **BC**, CA, AC
2	Mild	BA, BB, AB
1	None	AA

- **Rank 3** would be transferred to the 4-Digit Diagnostic Code Grid on page 1 of the FASD Diagnostic Form (as duplicated below).

Result:

4-Digit Diagnostic Code Grid



III. Instructions for Deriving the 4-Digit Code

B.2. Ranking the Facial Phenotype

The FAS Facial Phenotype

The face of FAS is distinguished by the simultaneous expression of three facial features:

1. Small palpebral fissure lengths (2 or more standard deviations below the mean) (Figure 2)
2. Smooth Philtrum (Rank 4 or 5 on the Lip-Philtrum Guide) (Figure 3).
3. Thin upper lip (Rank 4 or 5 on the Lip-Philtrum Guide) (Figure 3).

David Smith, M.D., who coined the term FAS in 1973, identified these features as the *key* diagnostic facial features in 1979 (Smith, 1979). A series of analytic studies conducted 20 years later confirmed the sensitivity and specificity of these features to FAS, and served to case-define the magnitude of expression required to maximize sensitivity (100%) and specificity (99%) (Astley & Clarren, 1996, 2000, 2001). Relaxation of these criteria substantially reduces sensitivity and specificity. The clinical validity of these features has been confirmed through population-based screening and surveillance studies (Astley et al., 2002; Astley, 2004) and empirical studies documenting remarkably strong correlations between these midline facial anomalies and underlying brain damage/dysfunction (Astley & Clarren, 2001). As the FAS facial phenotype increases in severity of expression from Rank 1 to Rank 2 to Rank 3 to Rank 4, the prevalence of underlying brain damage/dysfunction also increases linearly. The FAS facial phenotype, including partial expressions of the phenotype, serves as a sensitive marker of brain damage/dysfunction.

How to Measure and Rank the Face: The 2nd Digit of the 4-Digit Diagnostic Code

There are two methods for measuring the facial features: 1) direct measurement and 2) computerized analysis of a digital facial photograph using the FAS Facial Photographic Analysis Software. The latter is the most accurate and is described in detail in Astley & Clarren (2001). The facial analysis software can be obtained from the FAS Diagnostic & Prevention Network website [http://depts.washington.edu/fasdpn]. The computerized method for analyzing facial features was designed to use a *standard* digital camera to maximize clinical access to this technology, while maintaining the highest level of accuracy. An instructional CD-ROM called FAS TUTOR ™ demonstrates how to accurately measure the facial features. It too can be obtained from the FAS DPN website.

A. Palpebral Fissure Length (PFL)

Direct measurement: The PFLs are measured to the nearest mm with a clear plastic, 15-cm ruler, held as close as possible to the eye without touching the eye or eye-lashes (Figures 1A, 1B). We choose not to use calipers because we find our patients are often too young and active to cooperate safely. The patient is asked to open their eyes fully to allow accurate identification of the endocanthion and exocanthion landmarks (Astley et al., 1999; Farkas, 1994). Epicanthal folds should be gently pulled to the midline to expose the endocanthion. It is difficult to obtain accurate measures of the PFL by direct measure. The physician should confirm the accuracy of their measurement technique against a gold standard (perhaps by measuring a colleague's PFL with a ruler that was previously measured with calipers). See the FAS-TUTOR CD for instructional animations (Astley et al.1999).

Computer measurement: A digital photo of the face is taken with a ¾ inch paper sticker placed between the eyebrows to serve as an internal measure of scale (Astley & Clarren, 2001). The photo is analyzed using the FAS Facial Photographic Analysis Software (Astley, 2003). The PFL is measured by clicking the mouse on the endocanthion and exocanthion landmarks of the right and left eyes. The length of each palpebral fissure and its z-score (number of standard deviations above or below the norm) are computed automatically based on formulas and normal charts embedded in the software. More detailed instructions are provided with the software.

Ranking*:* The PFL is ranked according to its z-score (or how many standard deviations above or below the mean it is on a normal anthropometric chart). If the eyes are substantially different in size, (more than 2 mm different) rank the larger PFL. If the eyes are comparable in size, rank the mean of the right and left PFL. Normal palpebral fissure length charts for Caucasians are provided in Section VIII (Hall et al., 1989). Normal PFL charts adjusted for race should be used if available and confirmed valid. There is general agreement among medical professionals that new more accurate and valid norms for palpebral fissure charts are needed. Until new charts are available, we have chosen to use the Hall Caucasian Charts for they reflect a composite of several published Caucasian charts and best reflect the rate of growth from birth to 16 years of age that we have observed among normally developing Caucasian children.

B. Upper Lip Thinness and Philtrum Smoothness

Direct measurement: Upper lip thinness (the red or vermilion portion of the upper lip) and philtrum smoothness are measured independent of one another using the 5-point pictorial Likert scale presented on the Lip-Philtrum Guides (Figure 3). Two Guides are available, one for Caucasians and one for African Americans. The Guide that best matches the phenotypic profile of the patient's race should be used. The physician holds the Lip-Philtrum Guide next to the patient's face and identifies the picture that best matches the patient's upper lip and identifies the picture that best matches the patient's philtrum. Lips must be *gently closed* with *no* smile to obtain accurate measures (Figure 4) (Astley et al., 1999). The physician's eyes must be in the patient's frankfort horizontal plane (represented by a line drawn from the external auditory canal through the lowest border of the bony orbital rim [orbitale]) to obtain accurate, standardized measures of upper lip thinness (Figure 5). This alignment is readily achieved with a handheld Guide. Stereotaxic equipment is not required.

Computer measurement: A digital photograph of the face is taken with the camera lens aligned in the patient's frankfort horizontal plane. The image is imported into the FAS Facial Photographic Analysis Software. The red (or vermilion) portion of the upper lip is outlined with the mouse to compute circularity (perimeter^2/area) (Figure 1). The thinner the upper lip, the greater the circularity (Figure 3). Circularity is not influenced by the size of the photograph. Each Rank on the Lip-Philtrum Guide is defined by a range of circularities (Figure 3). The software automatically ranks lip thinness using the circularity measure. The philtrum is measured by selecting the picture on the Lip-Philtrum Guide that best matches the patient's philtrum. More detailed instructions are provided with the software.

Figure 1. An example of the upper lip outlined to compute circularity. The circularity of this lip is 44.2, which is equivalent to Rank 2 on Lip-Philtrum Guide 1.

C. Deriving the Facial ABC-Score

Rank palpebral fissure length, philtrum smoothness, and upper lip thinness by circling A, B, or C in each column in the ABC-Score table at the bottom of page 2 of the FASD Diagnostic Form. This table is duplicated below as Table 3. The three facial features must be measured at the same age. In other words, one would NOT rank PFL at 10 years of age and philtrum and lip at 15 years of age. If facial measures are available at more than one age, rank the age when the FAS phenotype is expressed the most. If FAS features are never expressed, score the face between the ages of 3 and 10 years, or at any age if this age range is not available.

Table 3: Deriving the ABC-Score for Facial Phenotype

5-Point Likert Rank for Philtrum & Lip	Z-score* for Palpebral Fissure Length	Circle the ABC-Scores for: Palpebral Fissure	Philtrum	Upper Lip
4 or 5	≤ -2 SD	C	C	C
3	>-2 SD and ≤ -1 SD	B	B	B
1 or 2	> -1 SD	A	A	A

* Z-Score = (patient's PFL - mean PFL for normal population) / (standard deviation of mean PFL for normal population)

The z-score reflects how many standard deviations above or below the mean the patient's PFL is.

D. Deriving the 4-Digit Rank for Face

Next, refer to Table 4 to determine the *4-Digit Diagnostic Rank* based on the ABC-Score derived from Table 3. Transfer the resulting 4-Digit Diagnostic Rank for face to the 4-Digit Diagnostic Code Grid on page 1 of the FASD Diagnostic Form.

Table 4: Converting the Facial ABC-Score to a 4-Digit Diagnostic Rank for Face

4-Digit Diagnostic Rank	Level of Expression of FAS Facial Features	Palpebral Fissure - Philtrum - Lip ABC-Score Combinations
4	Severe	CCC
3	Moderate	CCB, CBC, BCC
2	Mild	CCA, CAC, CBB, CBA, CAB, CAA BCB, BCA, BBC, BAC ACC, ACB, ACA, ABC, AAC
1	None	BBB, BBA, BAB, BAA ABB, ABA, AAB, AAA

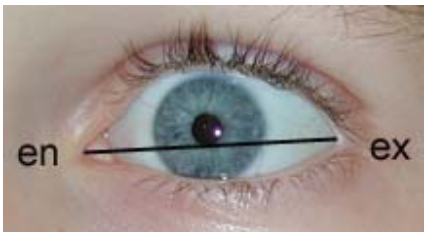


Figure 2A. Palpebral Fissure Length (PFL). Distance from endocanthion to exocanthion.

Figure 2B. PFL measured with a small ruler while patient looks up to fully expose exocanthion.

Lip-Philtrum Guide 1: Caucasian			ABC Scores		Lip-Philtrum Guide 2: African American		
	Upper Lip Circularity		Philtrum	Upper Lip	Upper Lip Circularity		
Rank	Range	Lip Pictured	Smoothness	Thinness	Lip Pictured	Range	Rank
5	≥ 131.5	178	C	C	80	≥ 62.1	5
4	131.4 to 75.5	85	C	C	57	62.0 to 52.1	4
3	75.4 to 57.5	65	B	B	39	52.0 to 30.1	3
2	57.4 to 42.5	50	A	A	29	30.0 to 27.5	2
1	≤ 42.4	35	A	A	25	≤ 27.4	1
Lip-Philtrum Guide 1							Lip-Philtrum Guide 2

Figure 3. Lip-Philtrum Guides 1 and 2. Pictorial examples of the 5-point Likert scales and the ABC-Scale used to rank upper lip thinness and philtrum smoothness in Caucasians and African Americans. Circularity is perimeter^2/area and is measured using the FAS Facial Photographic Analysis software. Laminated Lip-Philtrum Guides with the Growth and Face Tables printed on the backside are available at http://depts.washington.edu/fasdpn.

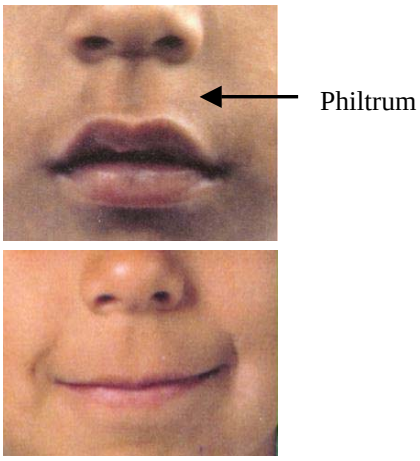


Figure 4. It is important that the patient have a relaxed facial expression (no smile). A smile can alter lip thinness and philtrum smoothness. This is the same person with and without a smile. Note that without the smile, the lip and philtrum would both receive a correct Likert rank of # 1 on the Caucasian Lip-Philtrum Guide 1. With a smile, the lip and philtrum would both receive an *incorrect* Likert rank of # 4.

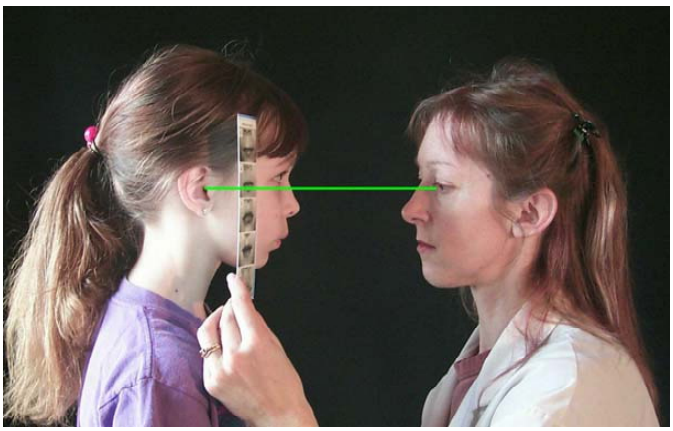


Figure 5. Illustration of a physician aligned in the patient's frankfort horizontal plane while using the Lip-Philtrum Guide to rank upper lip thinness and philtrum smoothness. The frankfort horizontal plane is defined by a line that passes through the patient's external auditory canal and the lowest border of the bony orbital rim (orbitale). The physician's eyes (or camera lens) should be directly in line with this plane. If the physician stood above this plane looking down on the patient, the patient's upper lip could appear thinner than it truly is.

Example: Ranking the Facial Phenotype

Patient Measurements at 10 Years of Age (Caucasian):

- Left PFL = 25.2 mm. Right PFL = 24.8 mm. Mean PFL = 25.0 mm
  Z-score = **-2.7** using Hall's PFL normal charts. (This means the PFL is 2.7 SDs below the norm)
  - Z-score = (25.0 – 28.7)/1.35 = -2.7.
  - Mean PFL for 10 years of age using Hall's Normal PFL chart = 28.7 mm.
  - 1 standard deviation on Hall's PFL normal chart = 1.35 mm.
  - The z-score is automatically computed by the FAS Facial Photographic Analysis Software.

- Philtrum smoothness received a **Rank 5** on the Caucasian Lip-Philtrum Guide (Figure 3).

- The circularity of the upper lip was 65.5. Thus, upper lip thinness received a **Rank 3** on the Caucasian Lip-Philtrum Guide (Figure 3). The circularity range for Rank 3 is 57.5 to 74.9.

Ranking

- The mean PFL z-score of -2.7 would receive an **ABC-Score = C** (≤ -2 SD) (Table 3).

- The Rank 5 philtrum would receive an **ABC-Score = C** (Table 3).

- The Rank 3 upper lip would receive an **ABC-Score = B** (Table 3).

- The ABC-Score combination for Palpebral Fissure - Philtrum - Lip would be **CCB** (Table 3).

Table 3: Deriving the ABC-Score for Facial Phenotype

5-Point Likert Rank for Philtrum & Lip	Z-score for Palpebral Fissure Length	Circle the ABC-Scores for: Palpebral Fissure	Philtrum	Upper Lip
4 or 5	≤ -2 SD	**C**	**C**	C
3	>-2 SD and ≤ -1 SD	B	B	**B**
1 or 2	> -1 SD	A	A	A

- The Facial ABC-Score of **CCB** reflects a **Moderate** level of expression of the FAS facial phenotype (Table 4).

- A **Moderate** expression of the FAS facial phenotype would receive a **Rank 3** in the 4-Digit Diagnostic (Table 4).

Table 4: Converting the Facial ABC-Score to a 4-Digit Diagnostic Rank

4-Digit Diagnostic Rank	Level of Expression of FAS Facial Features	Palpebral Fissure - Philtrum - Lip ABC-Score Combinations
4	Severe	CCC
3	**Moderate**	**CCB**, CBC, BCC
2	Mild	CCA, CAC, CBB, CBA, CAB, CAA, BCB, BCA, BBC, BAC ACC, ACB, ACA, ABC, AAC
1	None	BBB, BBA, BAB, BAA ABB, ABA, AAB, AAA

- **Rank 3** would be transferred to the 4-Digit Diagnostic Code Grid on page 1 of the FASD Diagnostic Form (as duplicated below).

Result:

4-Digit Diagnostic Code Grid

3 ____

Growth Deficiency	FAS Facial Features	CNS Damage		Growth	Face	CNS	Alcohol		Prenatal Alcohol
Severe	Severe	Definite	(4)					(4)	High risk
Moderate	Moderate	Probable	(3)		X			(3)	Some risk
Mild	Mild	Possible	(2)					(2)	Unknown
None	None	Unlikely	(1)					(1)	No Risk

III. Instructions for Deriving the 4-Digit Code

B.3. Ranking CNS

Alcohol's Impact on the Developing Brain

Alcohol is a teratogen that can alter the developing brain in a variety of ways from gross structural anomalies to subtle alterations in neurochemical levels (Stratton et al., 1996; West, 1986). Alterations in brain structure and/or chemistry can lead to altered brain function. Our ability to detect structural, neurological, and functional CNS abnormalities is dependent on the sensitivity of today's measurement tools, which will continue to improve over time. Not all structural or neurological abnormalities result in *measurable* dysfunction and not all functional abnormalities are due to underlying brain damage. Some functional abnormalities result from adverse postnatal environmental factors and are transient in nature if the environment is improved.

How to Rank CNS: The 3rd Digit of the 4-Digit Diagnostic Code

The 4-point Likert Scale for CNS documents: 1) that individuals with prenatal alcohol exposure can present with structural, neurological and/or functional CNS abnormalities; 2) that these CNS abnormalities occur along a continuum of severity; and 3) that not all functional abnormalities are due to underlying brain damage.

An important point to keep in mind is that the CNS scale performs as two scales in one. In its first use, the full scale (from 1 to 4) documents increasing "probability" of underlying CNS damage based on structural, neurological, and/or functional evidence. *The higher the Rank from 1 to 4, the stronger the evidence or higher the probability that there is underlying CNS damage*. In its second use, the scale (from 1 to 3) also documents increasing severity of brain dysfunction. *The higher the Rank from 1 to 3, the more severe and global the dysfunction.*

The descriptive labels assigned to Ranks 1 through 4 reflect the increasing probability that underlying CNS damage exists. Rank 4 is labeled "definite" because structural/neurological abnormalities are definitive evidence of CNS damage. Ranks 1, 2, and 3 are labeled "unlikely", "possible", and "probable" evidence of CNS damage, respectively, because measures of dysfunction are not definitive evidence of CNS damage, but the probability of underlying CNS damage increases with increasing severity of dysfunction. Data from the University of Washington FAS DPN show this to be true. Among the first 1,500 patients diagnosed, those presenting with Rank 2 or Rank 3-level dysfunction had a 5.8-fold and 10.8-fold increased risk of having structural/neurological damage, respectively, relative to patients with no evidence of dysfunction (Rank 1). As stated in the Institute of Medicine report (Stratton et al., 1996) "FAS can be characterized by behavioral or cognitive problems that are thought to result from *organic brain damage*, are not easily related to genetic background or environmental influences, and are resistant to improvement with traditionally effective intervention techniques".

All patients receive a Rank 1, 2 or 3 to document their level of brain dysfunction. Patients who present with significant structural and/or neurological evidence of CNS damage will also receive a Rank 4. Thus, all patients with structural/neurological evidence of CNS damage will have two CNS Ranks, one documenting their structural/neurological damage (Rank 4) and one documenting their level of dysfunction (Rank 1, 2 or 3). More specifically, they will receive either: (a) Ranks 4 and 3 (structural/neurological damage with Rank 3 level dysfunction); (b) Ranks 4 and 2 (structural/neurological damage with Rank 2 level delay/dysfunction); or (c) Ranks 4 and 1 (structural/neurological damage with no current evidence of delay/dysfunction). When two CNS Ranks are applicable, the 4-Digit Code and Diagnostic Category are based on the *highest* CNS rank received, for it reflects the highest level of certainty there is underlying CNS damage. Both CNS ranks would be marked by an '**X**' in the CNS Column of the Diagnostic Grid, but only the number of the highest rank would be inserted into the 4-Digit Code (See 4-Digit Diagnostic Code Grid below).

4-Digit Diagnostic Code Grid

						4				
Severe	Severe	Definite	(4)			X		(4)	High risk
Moderate	Moderate	Probable	(3)			X		(3)	Some risk
Mild	Mild	Possible	(2)					(2)	Unknown
None	None	Unlikely	(1)					(1)	No Risk
Growth Deficiency	**FAS Facial Features**	**CNS Damage**		Growth	Face	CNS	Alcohol		**Prenatal Alcohol**

Definitions of CNS Ranks 1 through 4.

CNS Rank 4: (Structural/Neurological Abnormalities)
"Definite" Evidence of CNS Damage.

Rank 4 Description: This rank is selected when the evidence for CNS damage is defined through a traditional medical approach. It is our impression that "brain damage" or static encephalopathy is readily diagnosed by physicians when 'significant' structural abnormalities of the brain are detected or when neurological findings of presumed prenatal origin are found.

Structural evidence of CNS damage may include, but is not limited to:

1. Microcephaly, defined as an occipital frontal circumference (OFC) 2 or more standard deviations below the mean. It is important to take race/ethnicity into consideration when assessing OFC. Head circumference 2 or more standard deviations below the mean has been associated with mental deficiency in the literature (Dolk, 1991; Pryor & Thelander, 1968).

2. Significant brain abnormalities of presumed prenatal origin observable through imaging techniques. Abnormalities may include, but are not limited to hydrocephaly, heterotopias, and change in shape and/or size of brain regions. These abnormalities should be determined by appropriately trained medical professionals.

Neurological evidence of CNS damage may include, but is not limited:

1. Seizures not due to a postnatal insult or other postnatal process.
2. Other hard neurological signs of presumed prenatal origin.

Rank 4 Criteria: At least one "significant" structural or neurological finding is required for a classification of CNS Rank 4 (Table 5). A significant finding is one that is 2 or more standard deviations below the norm if measured on a standardized scale or deemed "clinically significant" when assessed by an appropriate trained professional like a clinical radiologist or neurologist. Findings deemed significant should receive a Severity Score = 3 (see below).

Documenting the Evidence that Supports a Rank 4 Classification: Structural and neurological findings are recorded under the STRUCTURAL and NEUROLOGICAL headings of the CNS section (page 3) of the FASD Diagnostic Form. A 'Severity Score' is provided along the left margin of the Form to allow the clinical team to rank the severity of all structural and neurological findings. Only structural and/or neurological findings that receive a Severity Score = 3 (Significant) can contribute toward a CNS Rank 4 classification. For example, a seizure disorder not due to a postnatal insult would receive a Severity Score = 3. Often this type of seizure would warrant medical treatment. A seizure that occurred just once during a high fever would receive a Severity Score = 2. Absence of any seizure-like activity would receive a Severity Score = 1. An OFC $\leq$ -2 SDs ($\leq 2.5^{th}$ percentile) would receive a Severity Score = 3. An OFC > 2.5^{th} percentile and $\leq 10^{th}$ percentile would receive a Severity Score = 2. An OFC > 10^{th} percentile would receive a Severity Score = 1. This Severity Score allows one to rapidly scan the FASD Diagnostic Form and identify significant findings that support a Rank 4 classification.

CNS Rank 3: (Significant Dysfunction)
"Probable" Evidence of CNS Damage.

Rank 3 Description: Through our experience with hundreds of patients who have been exposed to potentially teratogenic doses of alcohol, we have found that many would not qualify as having static encephalopathy using the definition above, but neither could the possibility that they have static encephalopathy be dismissed out of hand. These patients typically have problems across multiple domains that may include, but are not limited to, executive function, memory, cognition, social/adaptive skills, academic achievement, language, motor, attention or activity level. These patients have problems that seem likely due to underlying brain damage rather than to adverse postnatal environmental experiences.

Rank 3 is selected based on evidence generated by standardized, validated psychometric assessments (e.g., WISC-III, WIAT-II, TOLD, PLS3, D-KEFS, VMI-II, etc), that are administered directly to the affected individual, or obtained from reliable informants, and interpreted by qualified professionals (e.g., psychologists, psychiatrists, occupational therapists, speech-language pathologists, etc). Rank 3 is assigned when this testing evidence documents "significant" impairment in three or more domains of brain function. "Significant" impairment is generally defined as performance 2 or more standard deviations below the mean (or its equivalent) on a standardized test. Developmental instruments, such as the Bayley Scales of Infant Development-II

would typically not be used as a source of psychometric data to support a classification of "static encephalopathy", for developmental delay is not always predictive of brain damage/dysfunction. The one exception to this rule would be developmental scores that are so low (e.g., Bayley Scales of Infant Development-II standard scores: MDI < 50, PDI < 50) that relevant literature finds these scores highly predictive of significant brain damage/dysfunction.

Rank 3 Criteria: "Significant" impairment across three or more domains of brain function is required for a classification of CNS Rank 3 (Table 5). Global delay, in which multiple domains are (by definition) affected, can comprise evidence for a Rank 3. Domains of brain function may include, but are not limited to: executive function, memory, cognition, social/adaptive skills, academic achievement, language, motor, attention or activity level. The "domains" of interest, in each diagnostic evaluation, are determined by the experienced clinical professionals involved in assessing the affected individual. Evidence to support a Rank 3 classification must come from standardized psychometric tests. "Significant" impairment is generally defined as performance 2 or more standard deviations below the norm on a standardized psychometric test.

Documenting the Evidence that Supports a Rank 3 Classification: The clinical team records which functional domains are delayed/impaired and which tests/scores support their decisions on the Functional Domains page (page 7) of the FASD Diagnostic Form. Evidence to support a Rank 3 classification must come from standardized psychometric tests. The outcomes of these psychometric tests are recorded on pages 3-5 of the FASD Diagnostic Form. A 'Severity Score' is provided along the left margin of the Functional Domains page (page 7) to allow the clinical team to rank the severity of delay/impairment for each assessed domain. A functional domain must receive a Severity Score = 3 (Significant) to contribute toward a Rank 3 classification. The Severity Score is described more fully below.

CNS Rank 2 (Mild to Moderate Delay/Dysfunction).
"Possible" Evidence of CNS Damage.

Rank 2 Description: This Rank should be given to two groups of patients, all of whom should have histories of behavioral, cognitive, and/or developmental problems. One group of patients is those who have not yet had the types of testing that would move them into Rank 3, if positive. The reason for lack of testing is usually because the patients are too young to be tested (typically less than 6 years of age). Children in this group should be re-assessed, when old enough, to rule out whether testing evidence meets criteria for CNS Rank 3. *Note that the term "neurobehavioral disorder" is assigned to CNS Rank 2. When this Rank is being assigned to young children based primarily on developmental data, the clinical team may decide to forego the use of the term "neurobehavioral disorder".* The other group of patients is those whose testing did not reveal compelling evidence for Rank 3 classification, but for whom, in the clinical team's judgment, the possibility of CNS damage cannot be wholly dismissed. In these cases, the behaviors of the patient cannot be conceptualized as, for example, normal variants or transient emotional responses to environmental problems. Alternative testing or alternative diagnostic assessment procedures should usually be considered. But if adequately sensitive and appropriate testing has been carried out without clear evidence of dysfunction or developmental delay, it is unlikely a Rank 2 classification would be given.

Rank 2 Criteria: Rank 2 reflects a range of delay and/or dysfunction that suggests the possibility of CNS damage. At the mild end of the Rank 2 range are those who present with developmental delay that, by clinical judgment, precludes a Rank 1 classification. At the severe end of the Rank 2 range are those who present with clear evidence of dysfunction, but the dysfunction is not sufficiently severe and wide-ranging to meet the criteria for Rank 3 (Table 5). A Rank 2, by definition, is assigned to all who fall between Ranks 1 and 3. Evidence to support a Rank 2 classification can come from standardized psychometric tests, observational data, and/or caregiver interview. Deficiencies (or definite differences from normative expectations) recorded in the FUNCTIONAL section (pages 3-7) of the FASD Diagnostic Form serve to support a Rank 2 classification.

Documenting the Evidence that Supports a Rank 2 Classification: The clinical team records which functional domains are delayed or impaired and which tests/scores support their decisions on the Functional Domains page (page 7) of the FASD Diagnostic Form. Evidence to support a Rank 2 classification can come from standardized psychometric tests, observational data, and/or caregiver interview. These data are recorded on pages 3-6 of the FASD Diagnostic Form. A 'Severity Score' is provided along the left margin of the Functional Domains page (page 7) to allow the clinical team to rank the severity of delay or impairment for each assessed domain. Typically a patient who meets the criteria for Rank 2 will have at least one domain with a Severity Score = 2 (mild to moderate delay or impairment), but less than three domains with a Severity Score = 3 (significant impairment). The Severity Score is described more fully below.

CNS Rank 1 (No Current Evidence of Delay/Dysfunction)
"No" Current Evidence of CNS Damage.

A Rank 1 classification is assigned when no functional or developmental problems are discerned that are likely to reflect CNS damage. Evidence to support a Rank 1 can come from standardized psychometric tests, observational data, and/or caregiver interview. While this classification is typically quite rare in an FASD Diagnostic Clinic, it might help to think of this outcome in the context of a well-child assessment conducted in a general pediatric clinic where most children would be classified as Rank 1.

Completing the CNS Section of the FASD Diagnostic Form

The CNS section appears on pages 3 through 7 of the FASD Diagnostic Form. These pages serve as a place to record pertinent structural, neurological, psychometric, and caregiver interview data available on the patient. Although space has been provided to record a full complement of assessments, we are not implying that all of these assessments must be conducted to derive a diagnosis. It is the responsibility of the clinical team to select the most appropriate assessment battery for an individual patient. Recording data for the structural, neurological, and psychometric sections is self-explanatory. The Caregiver Interview section, however, warrants further explanation.

An important aspect of the FASD evaluation is an in depth interview of the caregivers of the patient. This interview takes approximately one hour and is conducted by a qualified member(s) of the clinical team. At the University of Washington FAS DPN clinic, this interview is conducted jointly by the physician and psychologist while the patient is being formally assessed by the other clinical

team members. As in any diagnostic situation, once records are reviewed and there is a preliminary case formulation, the diagnostic interview will address several questions, such as: What are the problems that led to the diagnostic referral? What do the caregivers hope to gain from the assessment? What are the caregivers' views of the patient's overall strengths and weaknesses? What is the child's social and medical history, pertinent to this diagnostic evaluation? In an FASD diagnostic evaluation, we have found it very useful to also methodically ask questions that review age-appropriate functional abilities in areas that, according to the literature, are commonly problematic for alcohol-exposed individuals. These areas (planning/temporal skills, behavioral regulation/sensory motor integration, abstract thinking/judgment, memory/learning/information processing, spatial skills/spatial memory, social skills/adaptive behavior, and motor/oral motor control) are presented on the FASD Diagnostic Form (page 6). Routinely inquiring about the patient's capabilities in these areas serves several purposes. First, the caregivers' answers to these questions give insight into their interpretation of the patient's behaviors and about their general relationship with the patient. Second, it is often helpful to compare this subjective assessment to the psychometric profile. This can reveal information about the pattern of neurodevelopmental and neurobehavioral difficulties that standardized testing may miss, or provide evidence that is supportive of test results. The data recorded on page 6 of the Diagnostic Form are non-standardized observational measures.

Severity Score [0, 1, 2, 3]

Along the left margin of each CNS page is a Severity Score. This Severity Score serves two purposes. 1) It allows one to rapidly scan the left margin of the CNS pages to see what structural, neurological, and functional areas are most impacted. 2) The Severity Scores in the Structural/Neurological Sections and the Functional Domains page also serve to document what evidence was present to meet the criteria for CNS Ranks 2, 3, and 4, as described above. For example, at least one area in the Structural or Neurological Sections should have a Severity Score = 3 to meet criteria for a CNS Rank 4. At least three domains on the Functional Domains page should a Severity Score = 3 to meet criteria for a CNS Rank 3.

The clinical team ranks the level of impairment/abnormality as follows:

0	Unknown, Not Assessed
1	Within Normal Limits
2	Mild to Moderate
3	Significant

For outcomes measured on standardized scales, in general, outcomes two or more standard deviations below the norm would be judged significant, whereas outcomes between one and two standard deviations below the norm could be judged mild to moderate.

A comprehensive assessment will identify domains of strength, as well as domains with mild or significant impairment. Documenting the outcomes of all assessed domains, not just those with significant impairment, is important for treatment planning.

Table 5: Criteria for CNS Ranks 1 through 4

4-Digit Diagnostic Rank*	Probability of CNS Damage	Confirmatory Findings
4	Definite **Structural and/or Neurological Abnormalities** *Static Encephalopathy*	● Microcephaly: OFC 2 or more SDs below the norm. *and / or* ● Significant abnormalities in brain structure of presumed prenatal origin. *and / or* ● Evidence of hard neurological findings likely to be of prenatal origin.
3	Probable **Significant Dysfunction** *Static Encephalopathy*	● Significant impairment in three or more domains of brain function such as, but not limited to: cognition, achievement, memory, executive function, motor, language, attention, activity level, neurological 'soft' signs.
2	Possible **Mild to Moderate Delay or Dysfunction** *Neurobehavioral Disorder*	● Evidence of delay or dysfunction that suggest the possibility of CNS damage, but data to this point do not permit a Rank 3 classification.
1	Unlikely	● No current evidence of delay or dysfunction likely to reflect CNS damage.

* Transfer the resulting 4-Digit Diagnostic Rank for CNS to the 4-Digit Diagnostic Code Grid on page 1 of the FASD Diagnostic Form.

III. Instructions for Deriving the 4-Digit Code

B.4. Ranking Alcohol Exposure

Method for Ranking Alcohol: The 4th Digit of the 4-Digit Diagnostic Code

Alcohol exposure is ranked according to the quantity, timing, frequency, and certainty of exposure during pregnancy (Table 6). The case-definitions for the four Ranks address two important issues: 1) that exposure information in a clinical setting can be of limited availability or of unknown accuracy and 2) a clear consensus is not available concerning the amount of alcohol that can actually be toxic to each individual fetus (Stratton et al., 1996).

The case-definitions for prenatal alcohol exposure differentiate four clinically meaningful groups (Rank 4: confirmed exposure to high levels of alcohol; Rank 3: confirmed exposure, but the level is less than Rank 4 or the level is unknown; Rank 2: unknown exposure (neither confirmed absent nor confirmed present); and Rank 1: confirmed absence of exposure from conception to birth). High exposure is defined generally to be a blood alcohol concentration of greater than 100 mg/dL (a level that typically can be reached by a 55-kg woman consuming six to eight beers) weekly, early in pregnancy. In the absence of a clear consensus on the amount of alcohol that can actually be toxic to the fetus, this general definition should only serve as a guide, not a threshold.

One example of a 'Rank 4' exposure is the birth mother reported drinking to the point of intoxication weekly throughout pregnancy. Two examples of 'Rank 3' exposures include: 1) birth mother was observed to be drinking during pregnancy, but the amount is unknown, 2) birth mother reported drinking a glass of wine weekly, but stopped drinking as soon as she learned she was pregnant at 3 months. Two examples of when alcohol exposure is ultimately unknown and thus coded as Rank 2 include: 1) the child is adopted and the records are closed, and 2) the birth mother is known to have a problem with drinking, but there are no records or direct observation of her drinking during the index pregnancy. A Rank 1 classification (confirmed absence of drinking from conception to birth) is relatively rare in the general population since it is unlikely to occur unless a pregnancy is either planned or the woman never drinks.

Table 6: Criteria for Prenatal Alcohol Exposure Ranks 1 through 4

4-Digit Diagnostic Rank	Prenatal Alcohol Exposure Category	Description of Alcohol Use During Pregnancy
4	High Risk	● Alcohol use during pregnancy is CONFIRMED. *and* ● Exposure pattern is consistent with the medical literature placing the fetus at "high risk" (generally high peak blood alcohol concentrations delivered at least weekly in early pregnancy).
3	Some Risk	● Alcohol use during pregnancy is CONFIRMED. *and* ● Level of alcohol use is less than in Rank (4) or level is unknown.
2	Unknown Risk	● Alcohol use during pregnancy is UNKNOWN.
1	No Risk	● Alcohol use during pregnancy is CONFIRMED to be completely ABSENT from conception to birth.

Transfer the resulting 4-Digit Diagnostic Rank for Alcohol Exposure to the 4-Digit Diagnostic Code Grid on page 1 of the FASD Diagnostic Form.

III. Instructions for Deriving the 4-Digit

B.5. Ranking Other Pre- and Postnatal Exposures/Events

The Importance of Documenting Other Risk Factors

A comprehensive diagnostic process must take into consideration all other adverse prenatal and postnatal exposures and events, not just prenatal alcohol exposure. Many of the outcomes observed in individuals with prenatal alcohol exposure are not specific to (caused only by) prenatal alcohol exposure. A variety of other prenatal (poor prenatal care, prenatal complications, familial genetics, and exposure to other potentially teratogenic agents, etc.), and/or postnatal (physical/sexual abuse, disrupted placement histories, head injuries, chronic substance abuse by the patient, etc.) exposures and events could also contribute to the outcomes presented by the patient. The 4-Digit Diagnostic method requires the clinical team to record all pertinent prenatal and postnatal exposures and events on the standardized FASD Diagnostic Form, rank their severity using case-defined 4-point Likert scales, report them in the medical summary, and take them into consideration when deriving a diagnosis and intervention plan. It is important to note that the presence of other risk factors does not reduce the teratogenic potential of alcohol. When multiple risk factors are present, including prenatal alcohol exposure, each risk factor has the potential of being fully responsible, partially responsible, or not responsible at all for any particular outcome. The medical technology to determine which risk factor is responsible for which outcome simply does not exist at this point in time.

A. Prenatal Rank Definitions

Rank 4: High Risk

This Rank is reserved for alternate genetic conditions (e.g., Fragile X, velocardiofacial syndrome, down syndrome, etc.) or exposure to known teratogens (e.g., dilantin, valproic acid, etc.) that have been clearly shown to produce physical abnormalities.

Rank 3: Some Risk

This category is used for potential genetic conditions, exposures or prenatal conditions that have been associated with physical or neurodevelopmental problems in a less well-established way, when compared to those falling in Prenatal Rank 4. Examples of conditions that would be placed in this category would include poor prenatal care; patients whose parents have mild mental retardation, attention deficit disorders, significant learning disabilities or learning problems thought to be due to a non-specific (and non-teratogenic) source; prenatal exposure to drugs like marijuana or heroin, in otherwise non-specified frequencies and quantities; and cigarette smoking during pregnancy.

Rank 2: Unknown Risk

This category is used when the details of the family background and gestation are unknown – generally in the circumstance of a closed adoption.

Rank 1: No Known Risk

On occasion, the genetic, teratogenic, and prenatal histories are well documented and no factors can be identified that would explain the abnormalities found in the patient.

B. Postnatal Rank Definitions

Rank 4: High Risk

This Rank is used to note postnatal circumstances that have been shown to have a significant adverse effect on development in most instances. Examples would include clear physical and sexual abuse, multiple disrupted placements with clear impact on the child, neglect resulting in failure to thrive, serious head injury, or medical conditions which lead to brain damage (i.e. kernicterus or persistent neonatal apnea).

Rank 3: Some Risk

This Rank is used to note conditions akin to those in Rank 4, but the circumstances are less severe and so less likely to be a definite factor in the patient's present condition. Obviously, clinical judgment is needed in judging the magnitude of a postnatal problem and interpreting this information into a Rank 3 or 4 placement.

Rank 2: Unknown Risk

This Rank is used when historical information is missing. This is sometimes the case with adopted children or those in foster care. Adult patients may, at times, be unable to reconstruct their own early histories.

Rank 1: No Known Risk

This Rank is used when a well-documented history confirms an absence of adverse postnatal exposures/events.

IV. Diagnostic Categories

The 256 Diagnostic Codes can be logically grouped into 22 Diagnostic Categories

Category	Name
A	Fetal alcohol syndrome (alcohol exposed)
B	Fetal alcohol syndrome (alcohol exposure unknown)
C	Partial fetal alcohol syndrome (alcohol exposed)
D	Fetal alcohol syndrome phenocopy (no alcohol exposure)
E	Sentinel physical finding(s) / static encephalopathy (alcohol exposed)
F	Static encephalopathy (alcohol exposed)
G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
H	Neurobehavioral disorder (alcohol exposed)
I	Sentinel physical finding(s) (alcohol exposed)
J	No sentinel physical findings or CNS abnormalities detected (alcohol exposed)
K	Sentinel physical finding(s) / static encephalopathy (alcohol exposure unknown)
L	Static encephalopathy (alcohol exposure unknown)
M	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposure unknown)
N	Neurobehavioral disorder (alcohol exposure unknown)
O	Sentinel physical finding(s) (alcohol exposure unknown)
P	No sentinel physical findings or CNS abnormalities detected (alcohol exposure unknown)
Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
R	Static encephalopathy (no alcohol exposure)
S	Sentinel physical finding(s) / neurobehavioral disorder (no alcohol exposure)
T	Neurobehavioral disorder (no alcohol exposure)
U	Sentinel physical finding(s) (no alcohol exposure)
V	No sentinel physical findings or CNS abnormalities detected (no alcohol exposure)

V. 4-Digit Diagnostic Codes
Within each Diagnostic Category

Category	Diagnostic Name and Codes
A	Fetal alcohol syndrome (alcohol exposed) 2433 3433 4433 2434 3434 4434 2443 3443 4443 2444 3444 4444
B	Fetal alcohol syndrome (alcohol exposure unknown) 2432 3432 4432 2442 3442 4442
C	Partial fetal alcohol syndrome (alcohol exposed) 1333 1433 2333 3333 4333 1334 1434 2334 3334 4334 1343 1443 2343 3343 4343 1344 1444 2344 3344 4344
D	Fetal alcohol syndrome phenocopy (no alcohol exposure) 3431 4431 3441 4441
E	Sentinel physical finding(s) / static encephalopathy (alcohol exposed) 3133 3233 4133 4233 3134 3234 4134 4234 3143 3243 4143 4243 3144 3244 4144 4244
F	Static encephalopathy (alcohol exposed) 1133 1233 2133 2233 1134 1234 2134 2234 1143 1243 2143 2243 1144 1244 2144 2244
G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed) 1323 2323 3123 3323 4123 4323 1324 2324 3124 3324 4124 4324 1423 2423 3223 3423 4223 4423 1424 2424 3224 3424 4224 4424

Category	Diagnostic Name and Codes
H	Neurobehavioral disorder (alcohol exposed) 1123 1223 2123 2223 1124 1224 2124 2224
I	Sentinel physical finding(s) (alcohol exposed) 1313 2313 3113 3313 4113 4313 1314 2314 3114 3314 4114 4314 1413 2413 3213 3413 4213 4413 1414 2414 3214 3414 4214 4414
J	No physical findings or CNS abnormalities detected (alcohol exposed) 1113 1213 2113 2213 1114 1214 2114 2214
K	Sentinel physical finding(s) / static encephalopathy (alcohol exposure unknown) 1332 2332 3132 3332 4232 1342 2342 3142 3342 4242 1432 3232 4132 4332 1442 3242 4142 4342
L	Static encephalopathy (alcohol exposure unknown) 1132 1232 2132 2232 1142 1242 2142 2242
M	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposure unknown) 1322 2322 3122 3322 4122 4322 1422 2422 3222 3422 4222 4422
N	Neurobehavioral disorder (alcohol exposure unknown) 1122 1222 2122 2222
O	Sentinel physical finding(s) (alcohol exposure unknown) 1312 2312 3112 3312 4112 4312 1412 2412 3212 3412 4212 4412

Category	Diagnostic Name and Codes
P	No physical findings or CNS abnormalities detected (alcohol exposure unknown) 1112 2112 1212 2212
Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure) 1331 2331 3131 4131 1341 2341 3141 4141 1431 2431 3231 4231 1441 2441 3241 4241 3331 4331 3341 4341
R	Static encephalopathy (no alcohol exposure) 1131 1231 2131 2231 1141 1241 2141 2241
S	Sentinel physical finding(s) / neurobehavioral disorder (no alcohol exposure) 1321 2321 3121 3321 4121 4321 1421 2421 3221 3421 4221 4421
T	Neurobehavioral disorder (no alcohol exposure) 1121 2121 2221 1221
U	Sentinel physical finding(s) (no alcohol exposure) 1311 2311 3111 3311 4111 4311 1411 2411 3211 3411 4211 4411
V	No physical findings or CNS abnormalities detected (no alcohol exposure) 1111 2111 1211 2211

VI. 4-Digit Diagnostic Codes Sorted Numerically

Code	Category	Diagnostic Name
1111	V	No sentinel physical findings or CNS abnormalities detected (no alcohol exposure)
1112	P	No sentinel physical findings or CNS abnormalities detected (alcohol exposure unk.)
1113	J	No sentinel physical findings or CNS abnormalities detected (alcohol exposed)
1114	J	No sentinel physical findings or CNS abnormalities detected (alcohol exposed)
1121	T	Neurobehavioral disorder (no alcohol exposure)
1122	N	Neurobehavioral disorder (alcohol exposure unknown)
1123	H	Neurobehavioral disorder (alcohol exposed)
1124	H	Neurobehavioral disorder (alcohol exposed)
1131	R	Static encephalopathy (no alcohol exposure)
1132	L	Static encephalopathy (alcohol exposure unknown)
1133	F	Static encephalopathy (alcohol exposed)
1134	F	Static encephalopathy (alcohol exposed)
1141	R	Static encephalopathy (no alcohol exposure)
1142	L	Static encephalopathy (alcohol exposure unknown)
1143	F	Static encephalopathy (alcohol exposed)
1144	F	Static encephalopathy (alcohol exposed)
1211	V	No sentinel physical findings or CNS abnormalities detected (no alcohol exposure)
1212	P	No sentinel physical findings or CNS abnormalities detected (alcohol exposure unk.)
1213	J	No sentinel physical findings or CNS abnormalities detected (alcohol exposed)
1214	J	No sentinel physical findings or CNS abnormalities detected (alcohol exposed)
1221	T	Neurobehavioral disorder (no alcohol exposure)
1222	N	Neurobehavioral disorder (alcohol exposure unknown)
1223	H	Neurobehavioral disorder (alcohol exposed)
1224	H	Neurobehavioral disorder (alcohol exposed)
1231	R	Static encephalopathy (no alcohol exposure)
1232	L	Static encephalopathy (alcohol exposure unknown)
1233	F	Static encephalopathy (alcohol exposed)
1234	F	Static encephalopathy (alcohol exposed)
1241	R	Static encephalopathy (no alcohol exposure)
1242	L	Static encephalopathy (alcohol exposure unknown)
1243	F	Static encephalopathy (alcohol exposed)
1244	F	Static encephalopathy (alcohol exposed)
1311	U	Sentinel physical finding(s) (no alcohol exposure)
1312	O	Sentinel physical finding(s) (alcohol exposure unknown)
1313	I	Sentinel physical finding(s) (alcohol exposed)
1314	I	Sentinel physical finding(s) (alcohol exposed)
1321	S	Sentinel physical finding(s) / neurobehavioral disorder (no alcohol exposure)
1322	M	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposure unknown)
1323	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)

Code	Category	Diagnostic Name
1324	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
1331	Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
1332	K	Sentinel physical finding(s) / static encephalopathy (alcohol exposure unknown)
1333	C	Partial FAS (alcohol exposed)
1334	C	Partial FAS (alcohol exposed)
1341	Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
1342	K	Sentinel physical finding(s) / static encephalopathy (alcohol exposure unknown)
1343	C	Partial FAS (alcohol exposed)
1344	C	Partial FAS (alcohol exposed)
1411	U	Sentinel physical finding(s) (no alcohol exposure)
1412	O	Sentinel physical finding(s) (alcohol exposure unknown)
1413	I	Sentinel physical finding(s) (alcohol exposed)
1414	I	Sentinel physical finding(s) (alcohol exposed)
1421	S	Sentinel physical finding(s) / neurobehavioral disorder (no alcohol exposure)
1422	M	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposure unknown)
1423	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
1424	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
1431	Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
1432	K	Sentinel physical finding(s) / static encephalopathy (alcohol exposure unknown)
1433	C	Partial FAS (alcohol exposed))
1434	C	Partial FAS (alcohol exposed)
1441	Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
1442	K	Sentinel physical finding(s) / static encephalopathy (alcohol exposure unknown)
1443	C	Partial FAS (alcohol exposed)
1444	C	Partial FAS (alcohol exposed)
2111	V	No sentinel physical findings or CNS abnormalities detected (no alcohol exposure)
2112	P	No sentinel physical findings or CNS abnormalities detected (alcohol exposure unknown)
2113	J	No sentinel physical findings or CNS abnormalities detected (alcohol exposed)
2114	J	No sentinel physical findings or CNS abnormalities detected (alcohol exposed)
2121	T	Neurobehavioral disorder (no alcohol exposure)
2122	N	Neurobehavioral disorder (alcohol exposure unknown)
2123	H	Neurobehavioral disorder (alcohol exposed)
2124	H	Neurobehavioral disorder (alcohol exposed)
2131	R	Static encephalopathy (no alcohol exposure)
2132	L	Static encephalopathy (alcohol exposure unknown)
2133	F	Static encephalopathy (alcohol exposed)
2134	F	Static encephalopathy (alcohol exposed)
2141	R	Static encephalopathy (no alcohol exposure)
2142	L	Static encephalopathy (alcohol exposure unknown)
2143	F	Static encephalopathy (alcohol exposed)
2144	F	Static encephalopathy (alcohol exposed)
2211	V	No sentinel physical findings or CNS abnormalities detected (no alcohol exposure)
2212	P	No sentinel physical findings or CNS abnormalities detected (alcohol exposure unknown)
2213	J	No sentinel physical findings or CNS abnormalities detected (alcohol exposed)

Code	Category	Diagnostic Name
2214	J	No sentinel physical findings or CNS abnormalities detected (alcohol exposed)
2221	T	Neurobehavioral disorder (no alcohol exposure)
2222	N	Neurobehavioral disorder (alcohol exposure unknown)
2223	H	Neurobehavioral disorder (alcohol exposed)
2224	H	Neurobehavioral disorder (alcohol exposed)
2231	R	Static encephalopathy (no alcohol exposure)
2232	L	Static encephalopathy (alcohol exposure unknown)
2233	F	Static encephalopathy (alcohol exposed)
2234	F	Static encephalopathy (alcohol exposed)
2241	R	Static encephalopathy (no alcohol exposure)
2242	L	Static encephalopathy (alcohol exposure unknown)
2243	F	Static encephalopathy (alcohol exposed)
2244	F	Static encephalopathy (alcohol exposed)
2311	U	Sentinel physical finding(s) (no alcohol exposure)
2312	O	Sentinel physical finding(s) (alcohol exposure unknown)
2313	I	Sentinel physical finding(s) (alcohol exposed)
2314	I	Sentinel physical finding(s) (alcohol exposed)
2321	S	Sentinel physical finding(s) / neurobehavioral disorder (no alcohol exposure)
2322	M	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposure unknown)
2323	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
2324	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
2331	Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
2332	K	Sentinel physical finding(s) / static encephalopathy (alcohol exposure unknown)
2333	C	Partial FAS (alcohol exposed)
2334	C	Partial FAS (alcohol exposed)
2341	Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
2342	K	Sentinel physical finding(s) / static encephalopathy (alcohol exposure unknown)
2343	C	Partial FAS (alcohol exposed)
2344	C	Partial FAS (alcohol exposed)
2411	U	Sentinel physical finding(s) (no alcohol exposure)
2412	O	Sentinel physical finding(s) (alcohol exposure unknown)
2413	I	Sentinel physical finding(s) (alcohol exposed)
2414	I	Sentinel physical finding(s) (alcohol exposed)
2421	S	Sentinel physical finding(s) / neurobehavioral disorder (no alcohol exposure)
2422	M	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposure unknown)
2423	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
2424	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
2431	Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
2432	B	FAS (alcohol exposure unknown)
2433	A	FAS (alcohol exposed)
2434	A	FAS (alcohol exposed)
2441	Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
2442	B	FAS (alcohol exposure unknown)
2443	A	FAS (alcohol exposed)

Code	Category	Diagnostic Name
2444	A	FAS (alcohol exposed)
3111	U	Sentinel physical finding(s) (no alcohol exposure)
3112	O	Sentinel physical finding(s) (alcohol exposure unknown)
3113	I	Sentinel physical finding(s) (alcohol exposed)
3114	I	Sentinel physical finding(s) (alcohol exposed)
3121	S	Sentinel physical finding(s) / neurobehavioral disorder (no alcohol exposure)
3122	M	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposure unknown)
3123	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
3124	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
3131	Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
3132	K	Sentinel physical finding(s) / static encephalopathy (alcohol exposure unknown)
3133	E	Sentinel physical finding(s) / static encephalopathy (alcohol exposed)
3134	E	Sentinel physical finding(s) / static encephalopathy (alcohol exposed)
3141	Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
3142	K	Sentinel physical finding(s) / static encephalopathy (alcohol exposure unknown)
3143	E	Sentinel physical finding(s) / static encephalopathy (alcohol exposed)
3144	E	Sentinel physical finding(s) / static encephalopathy (alcohol exposed)
3211	U	Sentinel physical finding(s) (no alcohol exposure)
3212	O	Sentinel physical finding(s) (alcohol exposure unknown)
3213	I	Sentinel physical finding(s) (alcohol exposed)
3214	I	Sentinel physical finding(s) (alcohol exposed)
3221	S	Sentinel physical finding(s) / neurobehavioral disorder (no alcohol exposure)
3222	M	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposure unknown)
3223	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
3224	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
3231	Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
3232	K	Sentinel physical finding(s) / static encephalopathy (alcohol exposure unknown)
3233	E	Sentinel physical finding(s) / static encephalopathy (alcohol exposed)
3234	E	Sentinel physical finding(s) / static encephalopathy (alcohol exposed)
3241	Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
3242	K	Sentinel physical finding(s) / static encephalopathy (alcohol exposure unknown)
3243	E	Sentinel physical finding(s) / static encephalopathy (alcohol exposed)
3244	E	Sentinel physical finding(s) / static encephalopathy (alcohol exposed)
3311	U	Sentinel physical finding(s) (no alcohol exposure)
3312	O	Sentinel physical finding(s) (alcohol exposure unknown)
3313	I	Sentinel physical finding(s) (alcohol exposed)
3314	I	Sentinel physical finding(s) (alcohol exposed)
3321	S	Sentinel physical finding(s) / neurobehavioral disorder (no alcohol exposure)
3322	M	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposure unknown)
3323	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
3324	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
3331	Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
3332	K	Sentinel physical finding(s) / static encephalopathy (alcohol exposure unknown)
3333	C	Partial FAS (alcohol exposed)

Code	Category	Diagnostic Name
3334	C	Partial FAS (alcohol exposed)
3341	Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
3342	K	Sentinel physical finding(s) / static encephalopathy (alcohol exposure unknown)
3343	C	Partial FAS (alcohol exposed)
3344	C	Partial FAS (alcohol exposed)
3411	U	Sentinel physical finding(s) (no alcohol exposure)
3412	O	Sentinel physical finding(s) (alcohol exposure unknown)
3413	I	Sentinel physical finding(s) (alcohol exposed)
3414	I	Sentinel physical finding(s) (alcohol exposed)
3421	S	Sentinel physical finding(s) / neurobehavioral disorder (no alcohol exposure)
3422	M	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposure unknown)
3423	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
3424	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
3431	D	FAS phenocopy (no alcohol exposure)
3432	B	FAS (alcohol exposure unknown)
3433	A	FAS (alcohol exposed)
3434	A	FAS (alcohol exposed)
3441	D	FAS phenocopy (no alcohol exposure)
3442	B	FAS (alcohol exposure unknown)
3443	A	FAS (alcohol exposed)
3444	A	FAS (alcohol exposed)
4111	U	Sentinel physical finding(s) (no alcohol exposure)
4112	O	Sentinel physical finding(s) (alcohol exposure unknown)
4113	I	Sentinel physical finding(s) (alcohol exposed)
4114	I	Sentinel physical finding(s) (alcohol exposed)
4121	S	Sentinel physical finding(s) / neurobehavioral disorder (no alcohol exposure)
4122	M	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposure unknown)
4123	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
4124	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
4131	Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
4132	K	Sentinel physical finding(s) / static encephalopathy (alcohol exposure unknown)
4133	E	Sentinel physical finding(s) / static encephalopathy (alcohol exposed)
4134	E	Sentinel physical finding(s) / static encephalopathy (alcohol exposed)
4141	Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
4142	K	Sentinel physical finding(s) / static encephalopathy (alcohol exposure unknown)
4143	E	Sentinel physical finding(s) / static encephalopathy (alcohol exposed)
4144	E	Sentinel physical finding(s) / static encephalopathy (alcohol exposed)
4211	U	Sentinel physical finding(s) (no alcohol exposure)
4212	O	Sentinel physical finding(s) (alcohol exposure unknown)
4213	I	Sentinel physical finding(s) (alcohol exposed)
4214	I	Sentinel physical finding(s) (alcohol exposed)
4221	S	Sentinel physical finding(s) / neurobehavioral disorder (no alcohol exposure)
4222	M	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposure unknown)
4223	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
4224	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)

Code	Category	Diagnostic Name
4231	Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
4232	K	Sentinel physical finding(s) / static encephalopathy (alcohol exposure unknown)
4233	E	Sentinel physical finding(s) / static encephalopathy (alcohol exposed)
4234	E	Sentinel physical finding(s) / static encephalopathy (alcohol exposed)
4241	Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
4242	K	Sentinel physical finding(s) / static encephalopathy (alcohol exposure unknown)
4243	E	Sentinel physical finding(s) / static encephalopathy (alcohol exposed)
4244	E	Sentinel physical finding(s) / static encephalopathy (alcohol exposed)
4311	U	Sentinel physical finding(s) (no alcohol exposure)
4312	O	Sentinel physical finding(s) (alcohol exposure unknown)
4313	I	Sentinel physical finding(s) (alcohol exposed)
4314	I	Sentinel physical finding(s) (alcohol exposed)
4321	S	Sentinel physical finding(s) / neurobehavioral disorder (no alcohol exposure)
4322	M	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposure unknown)
4323	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
4324	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
4331	Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
4332	K	Sentinel physical finding(s) / static encephalopathy (alcohol exposure unknown)
4333	C	Partial FAS (alcohol exposed)
4334	C	Partial FAS (alcohol exposed)
4341	Q	Sentinel physical finding(s) / static encephalopathy (no alcohol exposure)
4342	K	Sentinel physical finding(s) / static encephalopathy (alcohol exposure unknown)
4343	C	Partial FAS (alcohol exposed)
4344	C	Partial FAS (alcohol exposed)
4411	U	Sentinel physical finding(s) (no alcohol exposure)
4412	O	Sentinel physical finding(s) (alcohol exposure unknown)
4413	I	Sentinel physical finding(s) (alcohol exposed)
4414	I	Sentinel physical finding(s) (alcohol exposed)
4421	S	Sentinel physical finding(s) / neurobehavioral disorder (no alcohol exposure)
4422	M	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposure unknown)
4423	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
4424	G	Sentinel physical finding(s) / neurobehavioral disorder (alcohol exposed)
4431	D	FAS phenocopy (no alcohol exposure)
4432	B	FAS (alcohol exposure unknown)
4433	A	FAS (alcohol exposed)
4434	A	FAS (alcohol exposed)
4441	D	FAS phenocopy (no alcohol exposure)
4442	B	FAS (alcohol exposure unknown)
4443	A	FAS (alcohol exposed)
4444	A	FAS (alcohol exposed)

VII. Clinical Summaries
For each of the 22 Diagnostic Categories

Clinical summaries for each of the 22 Diagnostic Categories are presented on the following pages listed alphabetically from A through V. A complete list of the 22 categories is presented in Section IV.

These summaries can be used as the first page of the final diagnostic report. They often require minor alterations or additions to conform to the specifics of an individual case.

A

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Fetal Alcohol Syndrome**
(2) Alcohol exposed

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of significant central nervous system (CNS) damage/dysfunction that occur in individuals exposed to alcohol during gestation. On the attached sheets are the specific findings in this patient's case that led to our conclusion that there was sufficient evidence to make the diagnosis of fetal alcohol syndrome.

Although we believe that the patient clearly has fetal alcohol syndrome, this does not mean that alcohol exposure during pregnancy is the only cause of the patient's current problems. A number of other factors could be contributing to the present situation, such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. Such factors may partly explain why there is so much variability in the kinds of specific difficulties that patients with FAS have.

Individuals with FAS have significant CNS damage/dysfunction and should be viewed as individuals with disabilities. The fetal alcohol syndrome diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific concerns that have been identified that need attention.

_____ _____
Physician's Signature Date

B

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Fetal Alcohol Syndrome**
(2) Alcohol exposure unknown

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of central nervous system (CNS) damage/dysfunction occurring in patients exposed to alcohol during gestation. On the attached sheets are the specific findings in this patient's case that led to our conclusion that there was sufficient evidence in this case to make a diagnosis of fetal alcohol syndrome even though the history of exposure to alcohol during gestation could not be confirmed.

Although we believe that the patient clearly has fetal alcohol syndrome, this does not mean that alcohol exposure during pregnancy is the only cause of the patient's current problems. A number of other factors could be contributing to the present issues, such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. Such factors may partly explain why there is so much variability in the kinds of specific difficulties that patients with FAS have.

Individuals with FAS have significant CNS damage/dysfunction and should be viewed as individuals with disabilities. The fetal alcohol syndrome diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific concerns that have been identified that need attention.

_____ _____
Physician's Signature Date

C

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Partial FAS**
(2) Alcohol exposed

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of central nervous system (CNS) damage/dysfunction occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS. Indeed, many patients who have been exposed to alcohol show most, but not all, of the classic features of this syndrome. We use the term "Partial FAS" when a patient's characteristic features are very close to the classic features of FAS and the alcohol history strongly suggests that alcohol exposure during gestation was at high risk and likely to have played a role in the syndrome. Patients with Partial FAS either have the full set of facial anomalies found with FAS and evidence of CNS damage/dysfunction, but do not have growth deficiency; or they have growth deficiency and evidence of CNS damage/dysfunction, and most, but not all of the FAS facial features. The severity of CNS damage/dysfunction is comparable between FAS and PFAS. As you can see from the enclosed list of features found in this patient, the patient meets the criteria for Partial FAS. Patients diagnosed with Partial FAS must have confirmed exposure to alcohol during gestation.

In addition to prenatal exposure to alcohol, a number of other factors could be contributing to the patient's current problems, such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. Such factors may partly explain why there is so much variability in the kinds of specific difficulties patients with Partial FAS experience.

Patients with Partial FAS have significant CNS damage/dysfunction and should be viewed as having a disability. The diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific concerns that have been identified that need attention.

_____ _____
Physician's Signature Date

D

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Fetal Alcohol Syndrome Phenocopy**
(2) No alcohol exposure

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of central nervous system (CNS) damage/dysfunction occurring in patients exposed to alcohol during gestation. On the attached sheets are the specific findings in this patient's case that led to our conclusion that the patient has all of the features of FAS. However, there is good reason to believe this patient was not exposed to alcohol during gestation.

Most syndromes can occasionally arise from an alternate cause. Presumably, this is the situation here. A number of other factors could be contributing to the present situation, such as the patient's genetic background and other potential exposures or problems during pregnancy, and various experiences since birth.

Whatever the cause of this patient's syndrome, he/she has structural, neurological and/or cognitive/behavioral problems and should be viewed as a person with a disability. This diagnosis has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific concerns that have been identified that need attention.

_____ _____
Physician's Signature Date

E

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Sentinel physical finding(s)**
(2) Static encephalopathy
(3) Alcohol exposed

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of central nervous system (CNS) damage/dysfunction in individuals exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, some but not all of the characteristic growth and facial features associated with FAS were present and there was evidence of CNS damage and/or dysfunction as you will see noted on the attached pages. There was also a clear history of exposure to significant amounts of alcohol during gestation. In this situation, we use the terms "static encephalopathy" and "Sentinel physical finding(s)" to describe the patient's condition. The patient's CNS abnormalities may include structural, neurological and/or functional problems. The diagnoses of "Static encephalopathy and Sentinel physical finding(s)" in the presence of alcohol exposure do not mean that alcohol is the only cause of the problem. A number of other factors could be contributing to the present issues such as the patient's genetic background, other potential exposures or problems during gestation, and various experiences since birth. These kinds of differences may partly explain why there is so much variability in the kinds of specific difficulties that patients with static encephalopathy and alcohol exposure have.

The diagnoses made today are based on the information available at the time of this assessment. If this patient's alcohol exposure was considered "low risk" and new information is uncovered which documents higher exposures; or if the patient's facial features, growth, or neurobehavioral problems were judged "probable" and further growth or development suggest a "definite" problem is present, then reconsideration of the diagnosis of fetal alcohol syndrome would be appropriate. Alternately other birth defect syndromes or conditions not related to alcohol exposure may also need reconsideration.

Individuals with significant CNS abnormalities have structural, neurological, and/or cognitive/behavioral problems and should be viewed as individuals with disabilities. The diagnosis of static encephalopathy has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

F

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Static encephalopathy**
(2) Alcohol exposed

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of central nervous system (CNS) damage/dysfunction occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, no growth deficiency or characteristic set of facial features were found so the patient does not have FAS, but there was evidence of significant CNS damage/dysfunction as you will see noted on the attached pages. There was also a clear history of exposure to significant amounts of alcohol during gestation. In this situation, we use the term "static encephalopathy" to describe the patient's condition. On the attached sheets are the specific findings in this patient's case that led us to this conclusion. The diagnosis of static encephalopathy does not mean that alcohol is the only cause of the problem. A number of other factors could be contributing to the present issues such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. These kinds of differences may partly explain why there is so much variability in the kinds of specific difficulties that patients with static encephalopathy face.

Individuals with significant CNS abnormalities have structural, neurological, and/or cognitive/behavioral evidence of CNS damage/dysfunction, and should be viewed as individuals with disabilities. The diagnosis of static encephalopathy has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

G

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Sentinel physical finding(s)**
(2) Neurobehavioral disorder
(3) Alcohol exposed

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of significant central nervous system (CNS) damage/dysfunction occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS. On the attached sheets you will find our specific observations in this case. We found that some, but not all, of the characteristic physical findings seen in patients with FAS were present. There was not strong evidence that the patient's cognitive/behavioral problems were clearly due to CNS damage, but there were suggestions that this was the case. In this situation we use the term "neurobehavioral disorder" to emphasize the possibility that the problems may not be entirely due to postnatal experiences. Certainly a number of other factors could be contributing to the patient's condition such as genetic background, other potential exposures or problems during pregnancy, and various experiences since birth.

The diagnoses made today are based on the information at hand. If further testing is done which makes the likelihood of significant CNS damage/dysfunction of prenatal cause more likely, then an alternate diagnosis could be considered. Alternately other birth defect syndromes or conditions not related to alcohol exposure may also need consideration.

In any event, the diagnosis of neurobehavioral disorder has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

H

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Neurobehavioral disorder**
(2) Alcohol exposed

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of significant central nervous system (CNS) damage/dysfunction in individuals exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

On the attached sheets you will find our specific observations in this case. There was not strong evidence that the patient's cognitive/behavioral problems were clearly due to CNS damage, but there were suggestions that this was the case. In this situation we use the term "neurobehavioral disorder" to emphasize the possibility that the problems may not be entirely due to postnatal experiences. Certainly a number of other factors could be contributing to the patient's condition such as genetic background, other potential exposures or problems during gestation, and various experiences since birth.

The diagnosis made today is based on the information available at the time of this assessment. If this patient's alcohol exposure was considered "low risk" and new information is uncovered which documents higher exposure, or if the patient's facial features or growth become more abnormal or if further testing finds further evidence of significant CNS damage/dysfunction, then further diagnostic consideration would be appropriate.

Whatever the cause, the diagnosis of neurobehavioral disorder has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

I

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Sentinel physical finding(s)**
(2) Alcohol exposed

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of significant central nervous system (CNS) damage/dysfunction occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS. Some individuals have the growth deficiency and/or facial characteristics, but do not have evidence of CNS damage/dysfunction. We refer to this condition as "Sentinel physical finding(s) / Alcohol exposed". On the attached sheets are the specific findings in this patient's case which indicate that the characteristic growth deficiencies and/or facial features are, to some extent, compatible with FAS, but at this time there is no clear evidence of cognitive or behavioral problems that strongly suggest CNS damage. At such time in the future that CNS damage/dysfunction is found through images of the brain, neurological testing or cognitive behavioral assessment, then the diagnosis of fetal alcohol syndrome should be reconsidered. Other birth defect syndromes that are not related to alcohol exposure should also be considered as alternate explanations for the patient's problems.

_____ _____

Physician's Signature Date

J

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis **(1) No sentinel physical findings or CNS abnormalities detected**
(2) Alcohol exposed

In this current assessment, we conclude that this patient was exposed to alcohol during gestation, but no specific cognitive, behavioral, or characteristic physical findings were detected in our examination.

No alcohol-related diagnoses are offered at this time. Re-evaluation would be appropriate in the future if problems arise that strongly suggest central nervous system (CNS) damage/dysfunction, growth deficiency, or facial dysmorphology.

_____ _____
Physician's Signature Date

K

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis
(1) Sentinel physical finding(s)
(2) Static encephalopathy
(3) Alcohol exposure unknown

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of significant central nervous system (CNS) damage/dysfunction in individuals exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, some but not all of the characteristic growth and facial features associated with FAS were present, and there was evidence of significant CNS damage/dysfunction as you will see noted on the attached pages. In this situation, we use the terms "Static encephalopathy" and "Sentinel physical finding(s)" to describe the patient's condition. Although it is unknown whether this patient was exposed to alcohol during gestation, a number of other factors could be contributing to the patient's current cognitive/behavioral problems such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. These kinds of differences may partly explain why there is so much variability in the kinds of specific difficulties that patients with CNS abnormalities have.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal, then further diagnostic consideration would be appropriate. Alternately other birth defect syndromes or conditions not related to alcohol exposure may also need reconsideration.

Individuals with significant static encephalopathy have evidence of CNS damage/dysfunction and should be viewed as a person with a disability. The diagnosis of static encephalopathy has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____

Physician's Signature Date

L

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Static encephalopathy**
(2) Alcohol exposure unknown

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of significant central nervous system (CNS) damage/dysfunction occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, no growth deficiency or characteristic set of facial features were found so the patient does not have FAS, but there was evidence of significant CNS damage/dysfunction as you will see noted on the attached pages. In this situation, we use the term "static encephalopathy" to describe the patient's condition. On the attached sheets are the specific findings in this patient's case that led us to this conclusion. Although it is unknown whether this patient was exposed to alcohol during gestation, a number of other factors could be contributing to the patient's current cognitive/behavioral problems such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. These kinds of differences may partly explain why there is so much variability in the kinds of specific difficulties patients with static encephalopathy face.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal, then further diagnostic consideration would be appropriate.

Individuals with static encephalopathy have evidence of CNS damage and/or dysfunction and should be viewed as individuals with disabilities. The diagnosis of static encephalopathy has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

M

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Sentinel physical finding(s)**
(2) Neurobehavioral disorder
(3) Alcohol exposure unknown

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of significant central nervous system (CNS) damage/dysfunction occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS. On the attached sheets you will find our specific observations in this case. We found that some, but not all, of the characteristic physical findings seen in patients with FAS were present and a confirmed history of alcohol exposure during gestation was not available. There was not strong evidence that the patient's cognitive/behavioral problems were clearly due to CNS damage, but there were suggestions that this was the case. In this situation we use the term "neurobehavioral disorder" to emphasize the possibility that the problems may not be entirely due to postnatal experiences. Certainly a number of other factors could be contributing to the patient's condition such as genetic background, other potential exposures or problems during pregnancy, and various experiences since birth.

The diagnoses made today are based on the information at hand. If further testing is done which makes the likelihood of significant CNS damage/dysfunction of prenatal cause more likely, then an alternate diagnosis would be considered. Alternately other birth defect syndromes or conditions not related to alcohol exposure may also need reconsideration.

In any event, the diagnosis of neurobehavioral disorder has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

N

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Neurobehavioral disorder**
(2) Alcohol exposure unknown

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of significant central nervous system (CNS) damage/dysfunction in individuals exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

On the attached sheets you will find our specific observations in this case. There was not strong evidence that the patient's cognitive/behavioral problems were clearly due to CNS damage, but there were suggestions that this was the case. In this situation we use the term "neurobehavioral disorder" to emphasize the possibility that the problems may not be entirely due to postnatal experiences. Certainly a number of other factors could be contributing to the patient's condition such as genetic background, other potential exposures or problems during gestation, and various experiences since birth.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal or if further testing finds further evidence of significant CNS damage/dysfunction, then further diagnostic consideration would be appropriate.

Whatever the cause, the diagnosis of neurobehavioral disorder has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____

Physician's Signature Date

O

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Sentinel physical finding(s)**
(2) Alcohol exposure unknown

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of significant central nervous system (CNS) damage/dysfunction occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

Some individuals have the growth deficiency and/or facial characteristics, but do not have evidence of CNS damage/dysfunction. We refer to this condition as "Sentinel physical finding(s)". On the attached sheets are the specific findings in this patient's case which indicate that the characteristic growth deficiencies and/or facial features are, to some extent, compatible with FAS, but alcohol exposure during gestation is unknown and at this time there is no clear evidence of CNS damage or dysfunction. At such time in the future that CNS damage/dysfunction is found through images of the brain, neurological testing or cognitive behavioral assessment, and a confirmed history of alcohol exposure is obtained, then further diagnostic consideration would be appropriate. Alternately other birth defect syndromes or conditions not related to alcohol exposure may also need reconsideration.

_____ _____
Physician's Signature Date

P

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis **(1) No sentinel physical findings or CNS abnormalities detected**
(2) Alcohol exposure unknown

In this current assessment, it is unknown whether or not this patient was exposed to alcohol during gestation. Furthermore, no specific cognitive, behavioral, or characteristic physical findings were detected in our examination.

No alcohol-related diagnoses are offered at this time. Re-evaluation would be appropriate in the future if further history of alcohol use in pregnancy is documented or problems arise that strongly suggested central nervous system (CNS) damage/dysfunction, growth deficiency, or facial dysmorphology.

_____ _____

Physician's Signature Date

Q

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis
(1) Sentinel physical finding(s)
(2) Static encephalopathy
(3) No alcohol exposure

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of significant central nervous system (CNS) damage/dysfunction in individuals exposed to alcohol during gestation.

In this patient's case, some but not all of the characteristic growth and facial features associated with FAS were present, there was evidence of significant CNS damage/dysfunction, and the patient was reportedly not exposed to alcohol during gestation. Based on these observations, which are documented on the attached pages, this patient does not have FAS, but does have significant CNS abnormalities and some of the physical characteristics found after alcohol exposure. A number of factors other than alcohol could be contributing to the patient's current cognitive/behavioral problems such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. The physical findings may suggest that other syndrome diagnoses be considered.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal, then further diagnostic consideration would be appropriate. . Alternately other birth defect syndromes or conditions not related to alcohol exposure may also need reconsideration.

Individuals with static encephalopathy have evidence of structural, neurological, and/or cognitive/behavioral deficits and should be viewed as a person with a disability. The diagnosis of static encephalopathy has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

R

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Static encephalopathy**
(2) No alcohol exposure

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of significant central nervous system (CNS) damage/dysfunction occurring in patients exposed to alcohol during gestation.

In this patient's case, no growth deficiency or characteristic set of facial features were found and the patient was not exposed to alcohol during gestation so the patient does not have FAS, but there was evidence of significant CNS damage/dysfunction as you will see noted on the attached pages. In this situation, we use the term "static encephalopathy" to describe the patient's condition. On the attached sheets are the specific findings in this patient's case that led us to this conclusion. A number of factors could be contributing to the patient's current cognitive/behavioral problems such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal, then further diagnostic consideration would be appropriate. . Alternately other birth defect syndromes or conditions not related to alcohol exposure may also need reconsideration.

Individuals with static encephalopathy have evidence of structural, neurological, and/or cognitive/behavioral deficits and should be viewed as a person with a disability. The diagnosis of static encephalopathy has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

S

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis
(1) Sentinel physical finding(s)
(2) Neurobehavioral disorder
(3) No alcohol exposure

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of significant central nervous system (CNS) damage/dysfunction occurring in patients exposed to alcohol during gestation.

On the attached sheets you will find our specific observations in this case. We found that some, but not all, of the sentinel physical finding(s) seen in patients with FAS were present and the patient was reportedly not exposed to alcohol during gestation. There was not strong evidence that the patient's cognitive/behavioral problems were clearly due to CNS damage, but there were suggestions that this may be the case. In this situation we use the term "neurobehavioral disorder" to emphasize the possibility that the problems may not be entirely due to postnatal experiences. The patient also had some of the physical characteristics often found with alcohol exposure. In this case, however, there was no alcohol exposure, therefore, these physical findings might suggest that other syndrome diagnoses be considered. Certainly a number of factors could be contributing to the patient's condition such as genetic background, other potential exposures or problems during pregnancy, and various experiences since birth.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal or if further testing finds further evidence of significant CNS damage/dysfunction, then further diagnostic consideration would be appropriate.

In any event, the diagnosis of neurobehavioral disorder has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

T

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Neurobehavioral disorder**
(2) No alcohol exposure

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of significant central nervous system (CNS) damage/dysfunction in individuals exposed to alcohol during gestation.

On the attached sheets you will find our specific observations in this case. In this patient's case, no growth deficiency or characteristic set of facial features were found and the patient was not exposed to alcohol during gestation so the patient does not have FAS. Although there was not strong evidence that the patient's cognitive/behavioral problems were clearly due to CNS damage, there were suggestions that this may be the case. In this situation we use the term "neurobehavioral disorder" to emphasize the possibility that the problems may not be entirely due to postnatal experiences. Certainly a number of other factors could be contributing to the patient's condition such as genetic background, other potential exposures or problems during gestation, and various experiences since birth.

The diagnosis made today is based on the information available at the time of this assessment. In the event that a confirmed history of alcohol exposure is obtained, or if the patient's facial features or growth become more abnormal or if further testing finds further evidence of significant CNS damage/dysfunction, then further diagnostic consideration would be appropriate. Alternately other birth defect syndromes or conditions not related to alcohol exposure may also need reconsideration.

Whatever the cause, the diagnosis of neurobehavioral disorder has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

_____ _____
Physician's Signature Date

U

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis: **(1) Sentinel physical finding(s)**
(2) No alcohol exposure

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of significant central nervous system (CNS) damage/dysfunction occurring in patients exposed to alcohol during gestation.

On the attached sheets are the specific findings in this patient's case which indicate that characteristic growth deficiencies and/or facial features, compatible with FAS, were present even though the patient was not exposed to alcohol during gestation. In this case, these physical findings might suggest that other syndrome diagnoses be considered.

At such time in the future that CNS damage/dysfunction is found through images of the CNS, neurological testing or cognitive behavioral assessment, and/or a confirmed history of alcohol exposure is obtained, then further diagnostic consideration would be appropriate. Alternately other birth defect syndromes or conditions not related to alcohol exposure may also need reconsideration.

_____ _____
Physician's Signature Date

V

THE FETAL ALCOHOL SYNDROME CLINIC
DIAGNOSTIC SUMMARY

Final Diagnosis **(1) No sentinel physical findings or CNS abnormalities detected**
(2) No alcohol exposure

In this current assessment, we conclude that this patient was not exposed to alcohol during gestation. Furthermore, no specific cognitive, behavioral, or characteristic physical findings were detected in our examination.

No diagnoses are offered at this time. Re-evaluation would be appropriate in the future if further history of alcohol use in pregnancy is documented or problems arise that strongly suggested central nervous system (CNS) damage/dysfunction, growth deficiency, or facial dysmorphology.

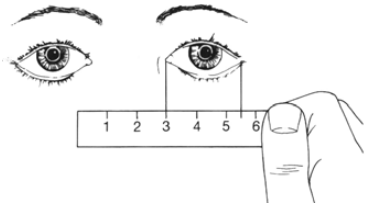
_____ _____

Physician's Signature Date

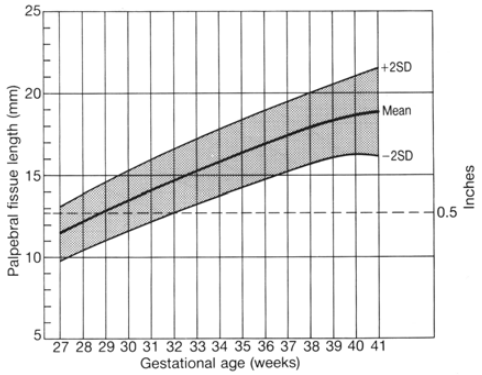
VIII. Reference Charts of Normal Growth

Provided for your convenience are normal anthropometric charts for palpebral fissure length, inner canthal distance, head circumference, height, and weight. Other valid growth charts may be used.

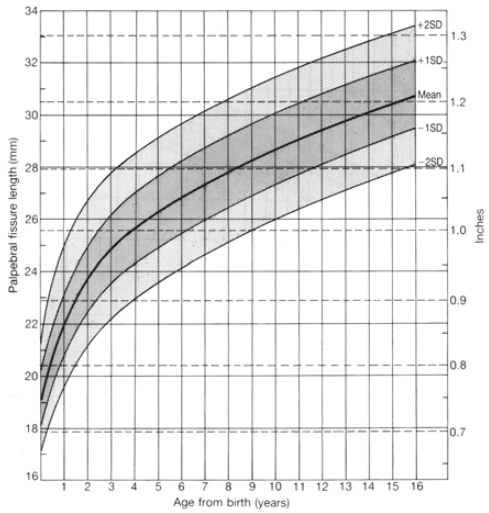
Palpebral Fissure Length



Measure from the endocanthion to the exocanthion.
Have patient look up, while holding head level, to standardize fissure measurement.



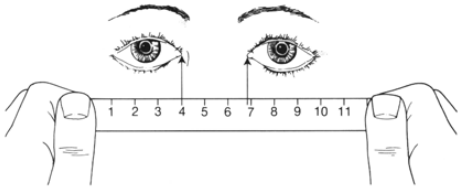
FEMALE and MALE (At Birth)



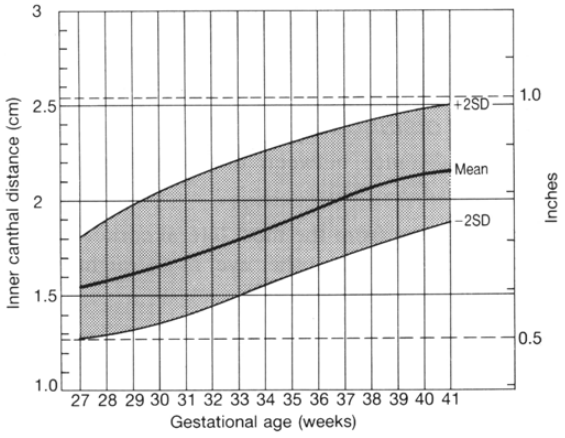
FEMALE and MALE (Birth to 16 years)

(Hall et. al., 1989, by permission)

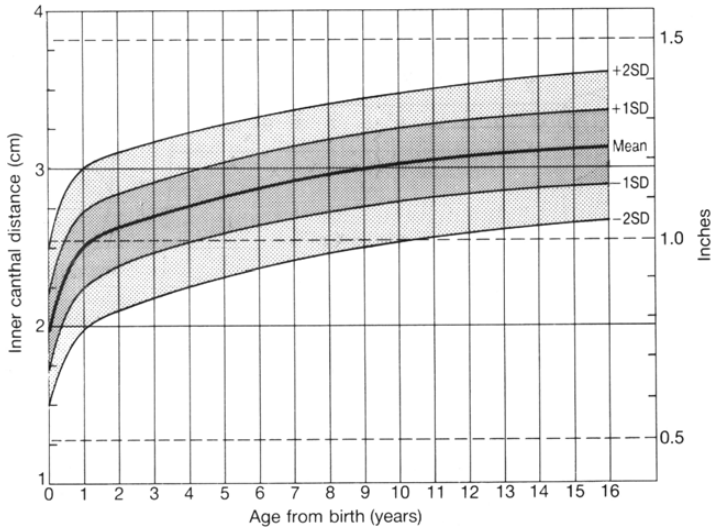
Inner Canthal Distance



Measure from the endocanthion of each eye, in a straight, line avoiding the curvature of the nose.



FEMALE and MALE (At Birth)

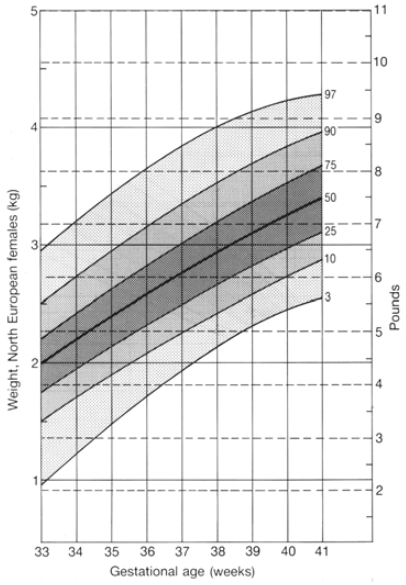


FEMALE and MALE (Birth to 16 years)

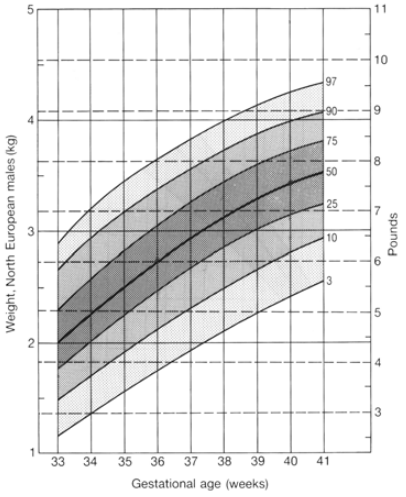
(Hall et. al., 1989, by permission)

Birth Weight

FEMALE



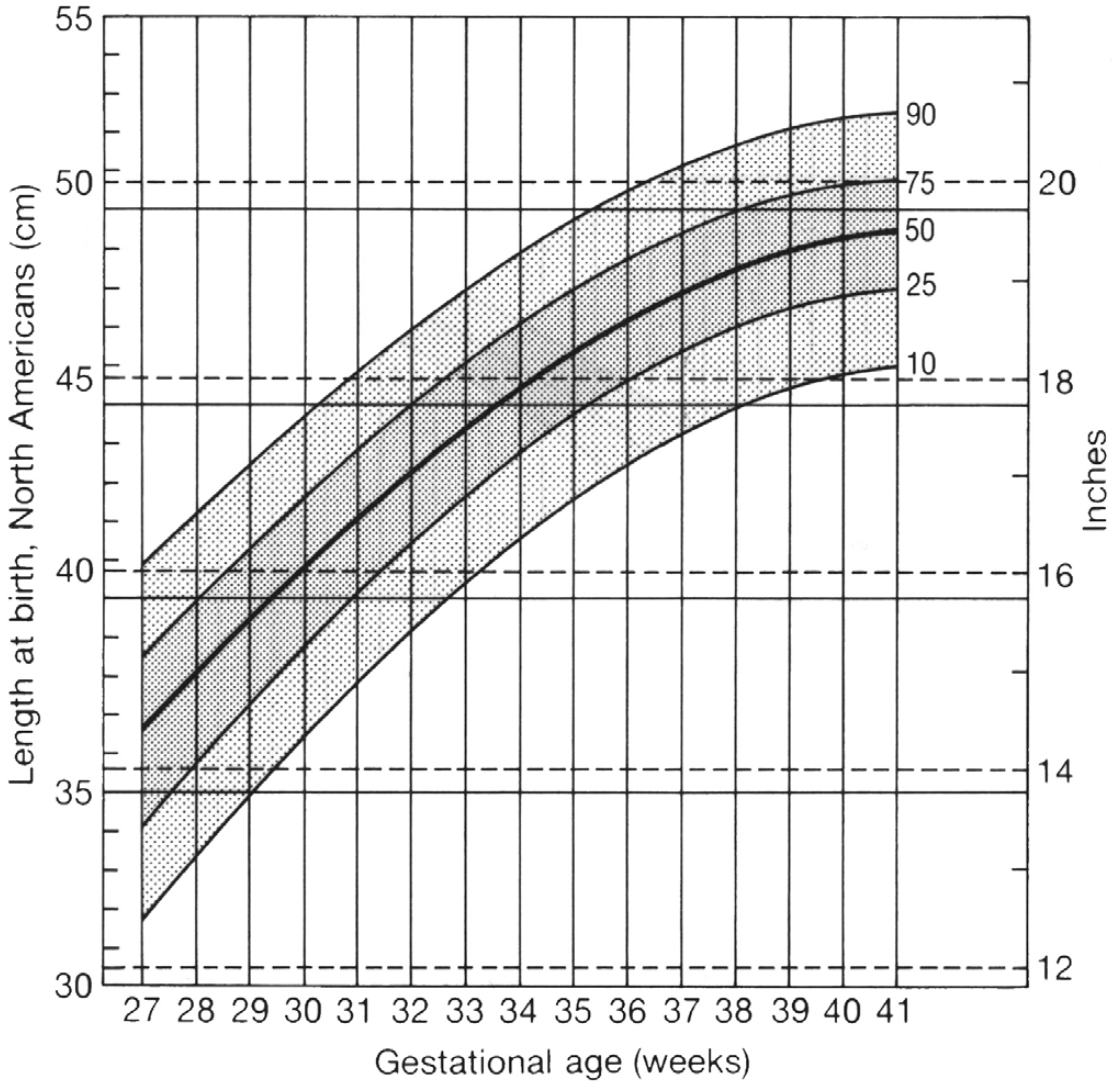
MALE



(Hall et. al., 1989, by permission)

Birth Length

FEMALE and MALE



(Hall et. al., 1989, by permission)

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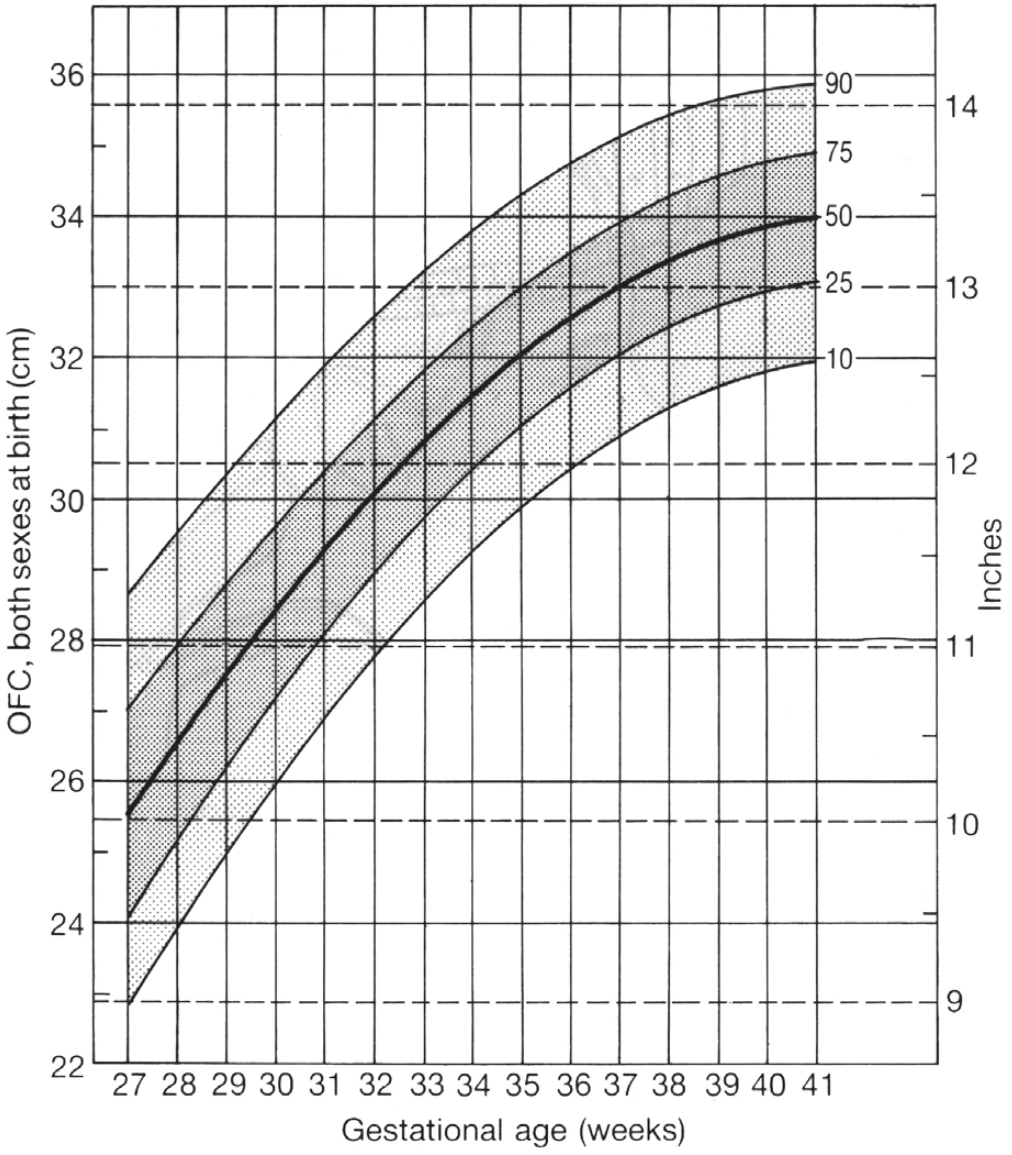
Head Circumference

At Birth

FEMALE and MALE

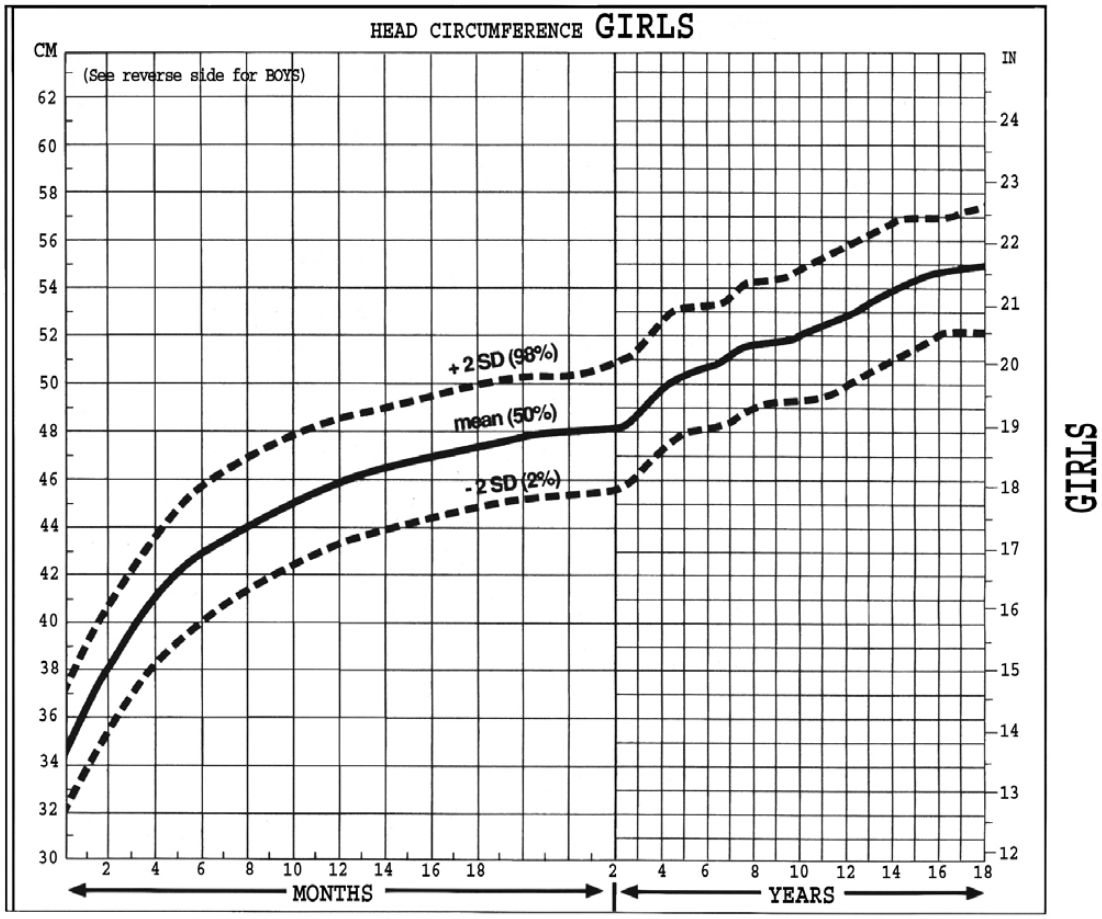


(Hall et. al., 1989, by permission)

Head Circumference

Birth to 18 years

FEMALE

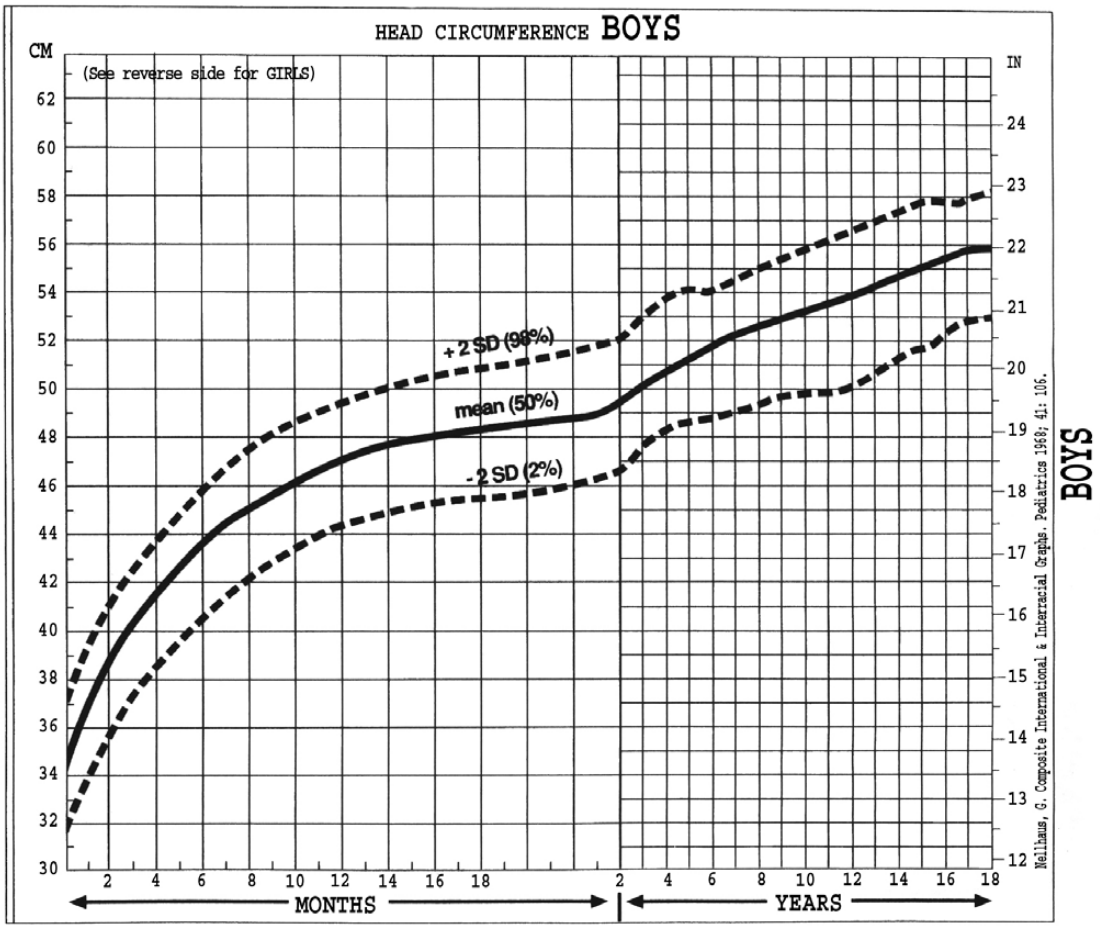


(Mead Johnson Nutritionals by permission, (Nellhaus, 1988)

Head Circumference

Birth to 18 years

MALE

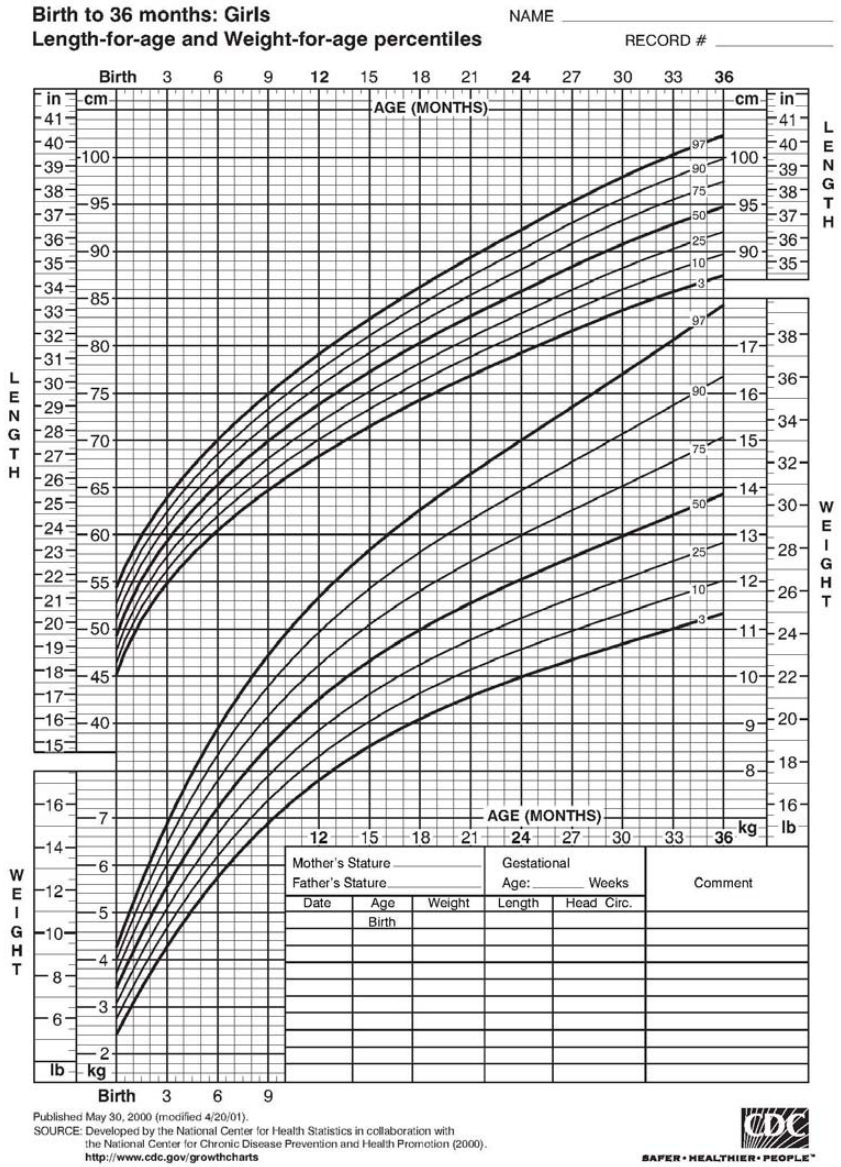


(Mead Johnson Nutritionals by permission, Nellhaus, 1988)

Height and Weight

Birth to 36 Months

FEMALE

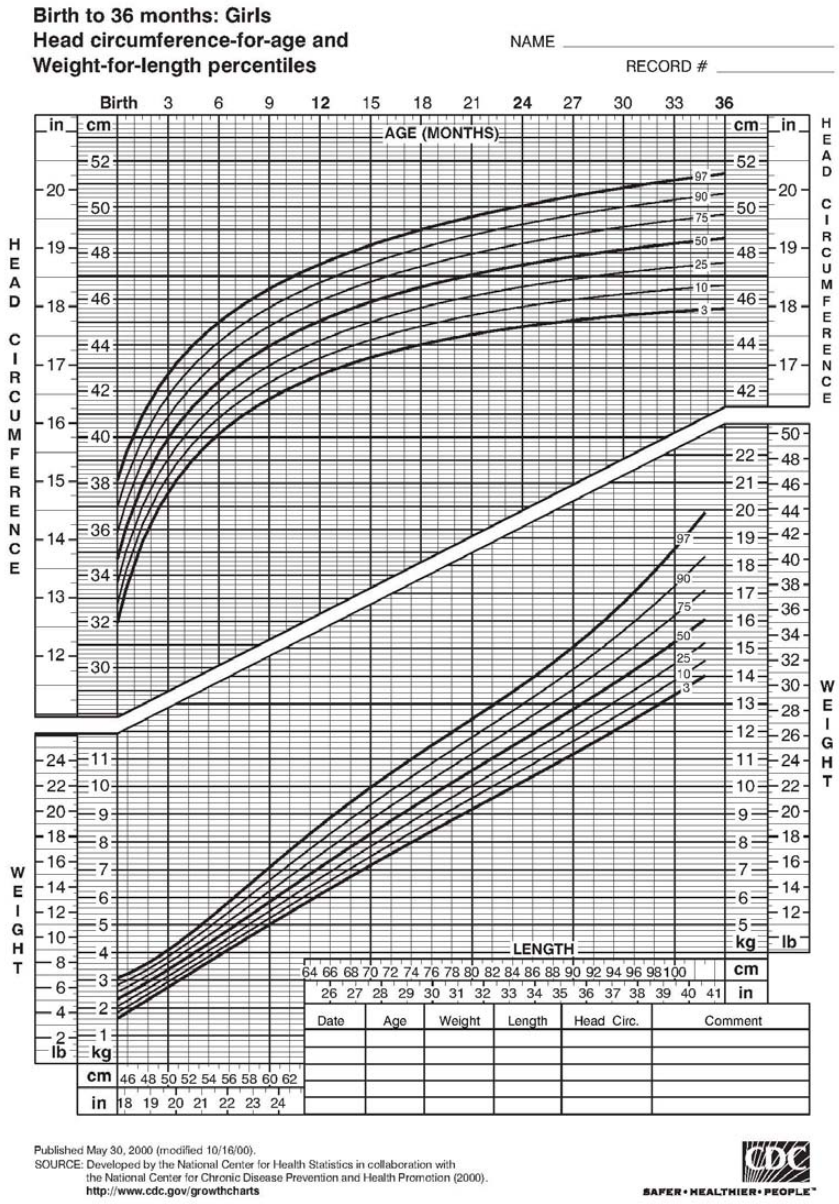


(CDC, 2000, http://cdc.gov/growthcharts)

Head Circumference

Birth to 36 Months

FEMALE

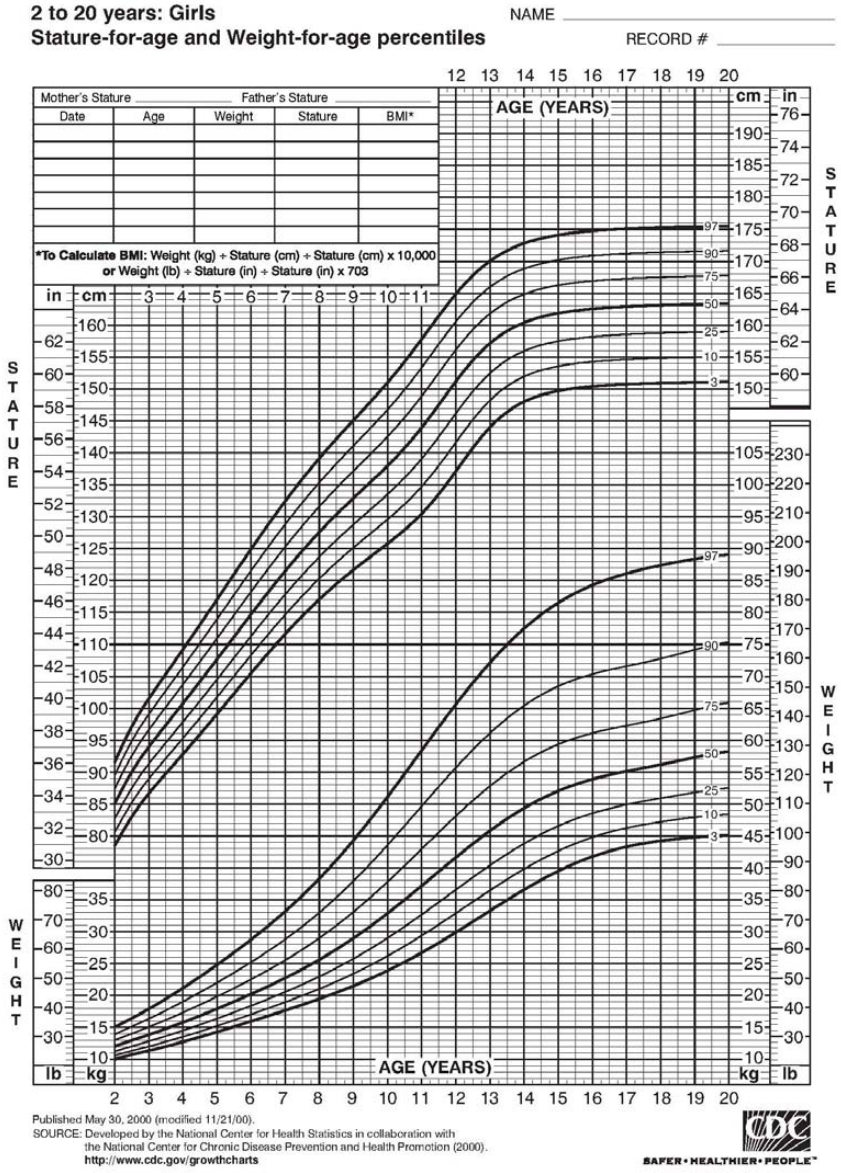


(CDC, 2000, http://cdc.gov/growthcharts)

Height and Weight

2 to 20 Years

FEMALE

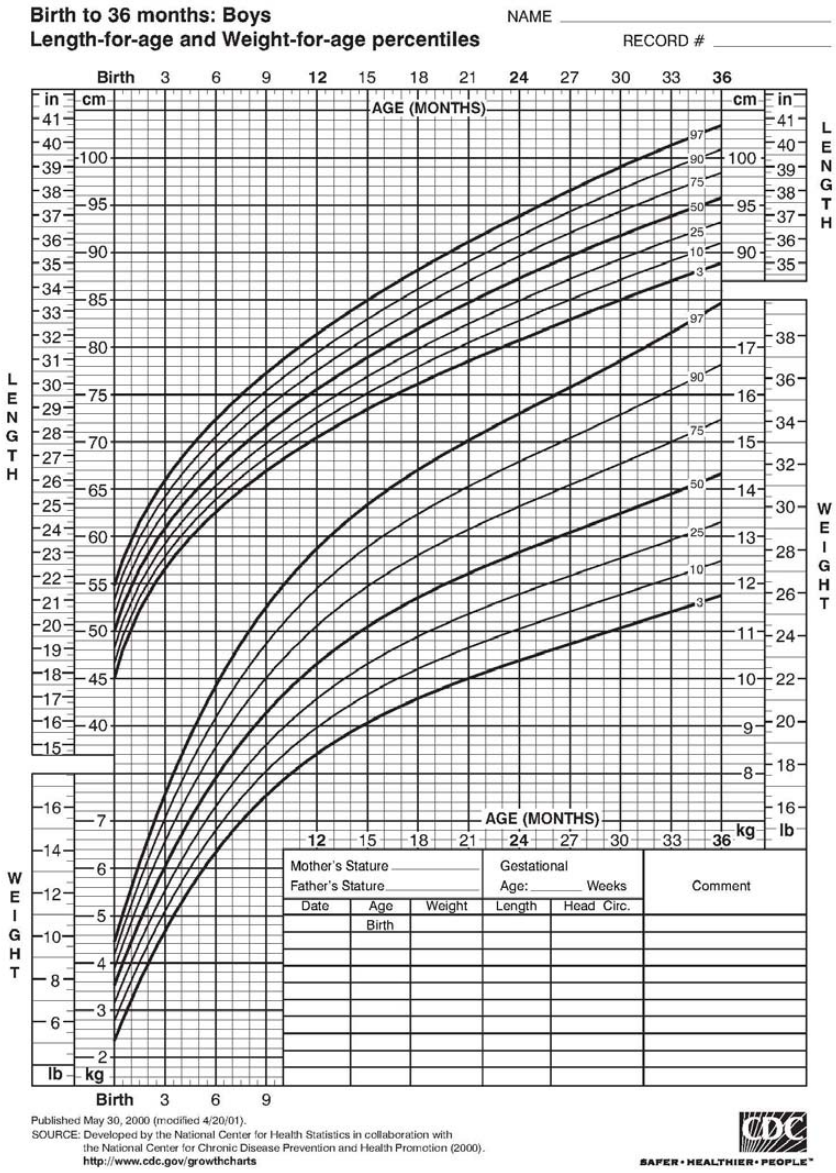


(CDC, 2000, http://cdc.gov/growthcharts)

Height and Weight

Birth to 36 Months

MALE

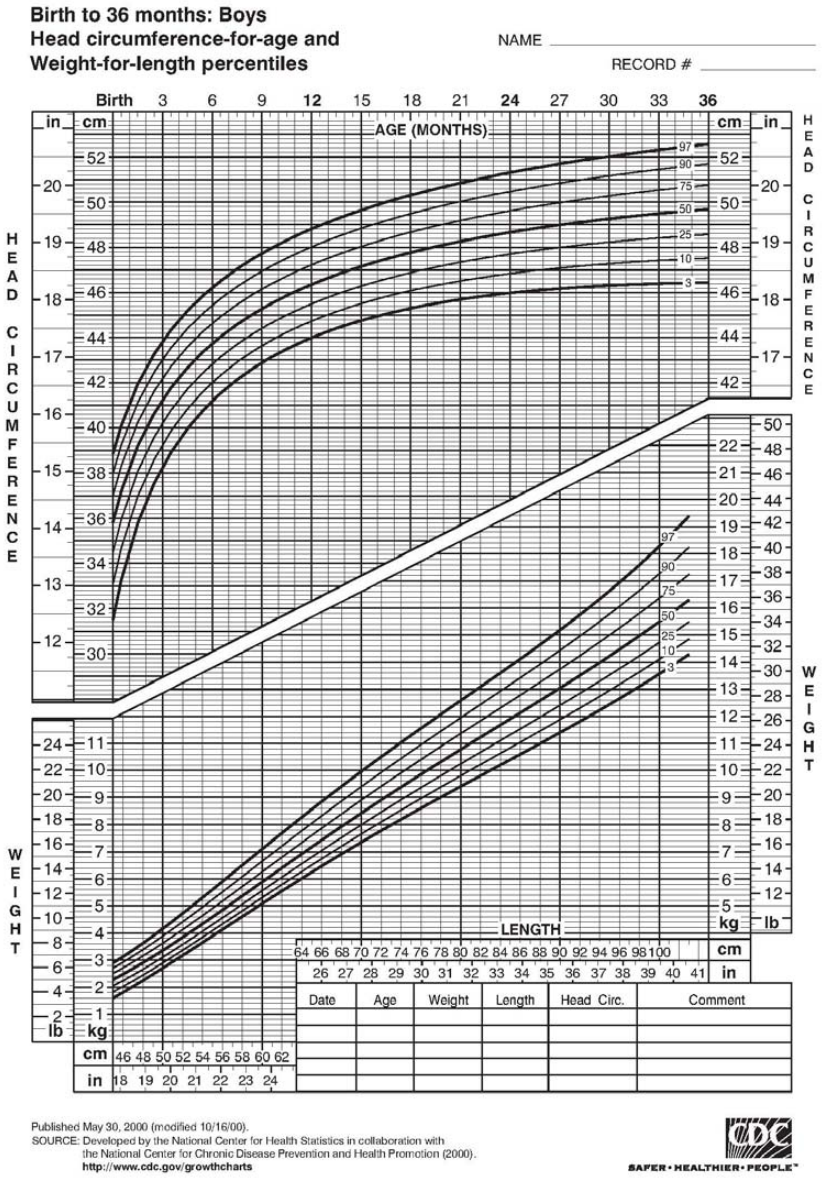


(CDC, 2000, http://cdc.gov/growthcharts)

Head Circumference

Birth to 36 Months

MALE

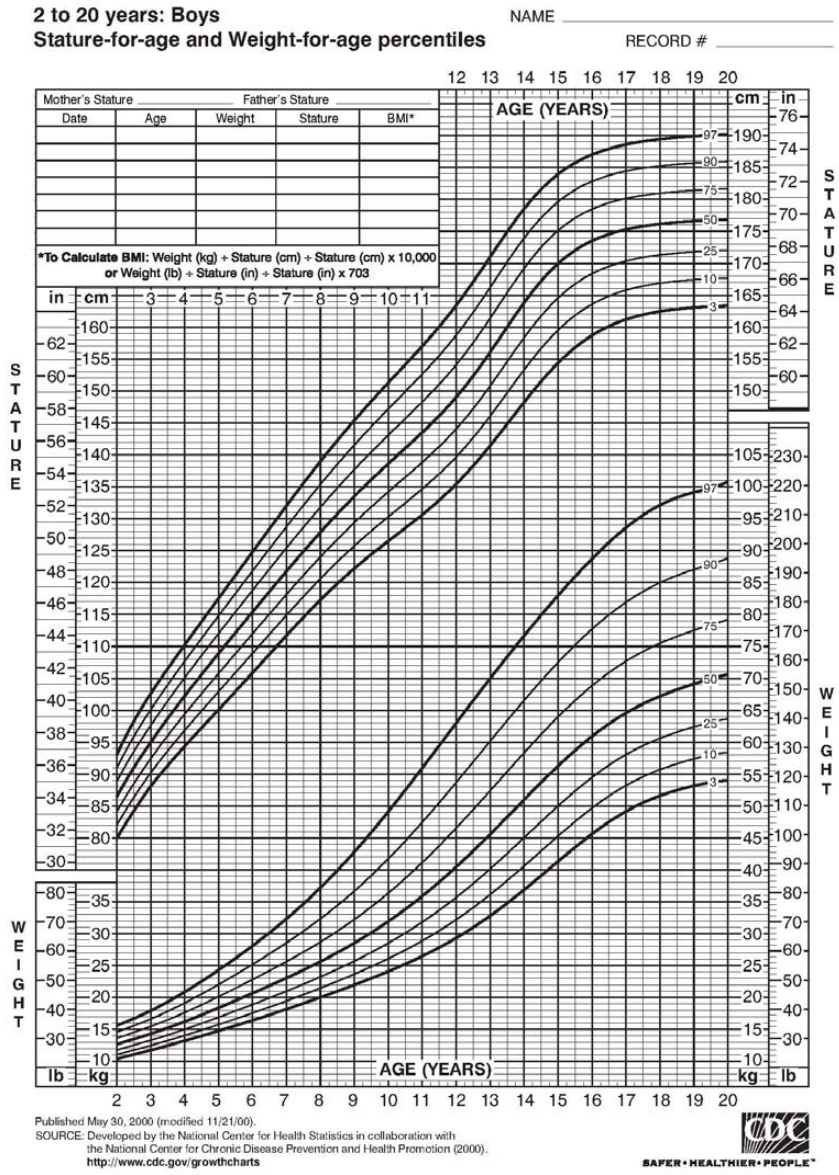


(CDC, 2000, http://cdc.gov/growthcharts)

Height and Weight

2 to 20 Years

MALE



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X. Appendices

1. FAS DPN WEBSITE http://depts.washington.edu/fasdpn

The University of Washington FAS DPN website provides a comprehensive overview of all clinical, research, and training activities conducted by the FAS DPN. Included are all publications, order forms for diagnostic tools, and registration forms for the training programs.

A. Frequently Asked Questions, Updates and Sample Forms.
Posted on the FAS DPN website are answers to frequently asked questions regarding the 4-Digit Code. Also posted are updates, support information and pdf versions of the FASD Diagnostic Form and NPIF. Examples of completed FASD Diagnostic Forms for selected 4-Digit Codes are also posted to further illustrate how to use the 4-Digit Code.

B. TRAINING PROGRAMS AND COURSES

i. Two-Day Interdisciplinary Clinical Training Program. This training program is offered twice a year at the University of Washington. Interdisciplinary clinical teams are taught how to use the 4-Digit Diagnostic Code in an interdisciplinary clinical setting.

ii. Online Training Course. This accredited course will provide healthcare, educational, and social service professionals with detailed instruction on the use of the 4-Digit Diagnostic Code in an interdisciplinary clinical setting.

iii. One-Day Clinical Observational Training Program. This training provides healthcare, social service, and educational professionals with insight into their role in the community for screening, referral, diagnosis, prevention, and intervention of FASD.

C. DIAGNOSTIC TOOLS AND SOFTWARE

i. FAS Facial Photographic Analysis Software (2003). This software is intended for use by healthcare and research professionals. The software allows one to measure the magnitude of expression of the key facial features of FAS from a digital facial photograph using the method derived by Astley & Clarren, (2001).

ii. FAS TUTOR ™ CD (1999). A compact disk entitled Fetal Alcohol Syndrome Tutor™ has been created by the University of Washington FAS DPN to instruct healthcare professionals, through video, computer animation, and photographic examples, on how to screen and diagnose FASD.

iii. Diagnostic Guide and Lip-Philtrum Guides (2004) Additional copies of the "*Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code, 2004*" and the laminated, *Lip-Philtrum Guides* can be ordered from the FAS DPN website.

2. NEW PATIENT INFORMATION FORM (See form below).
This form is sent to families requesting a diagnostic evaluation at the University of Washington FAS DPN clinic. The form allows the family to share with the clinic why they are seeking a diagnostic evaluation, what they hope to gain from the evaluation and what they currently know about the patient's exposure(s) and outcomes. This form serves as a clinical intake form.

New Patient Information Form FASD Clinic

Office Use: Date received ___/___/___ Deadline ___/___/___ ASAP ____ Response Let. ___/___/___ Photo ___ Screen Code _____
G _____ F _____ B _____ A _____ M _____: 1 2 3 4

Patient Identification

Patient's Social Security Number *(optional)* _____ ❑ Female ❑ Male Race _____

Patient's Name _____ Birth date _____ Age _____
First Middle Last

Patient's Address _____

City _____ County _____ State _____ zip code _____

Patient's Telephone Home ( ) _____ Work ( ) _____

Caretaker Identification

Name of patient's primary caretaker(s)_____

Relationship to patient: ❑ birth, ❑ adoptive, or ❑ foster parent ❑ other (specify _____)

Caretaker's Address

City _____ County _____ State _____ zip code _____

Telephone Home ( ) _____ Work ( ) _____

Name of patient's legal guardian(s) _____

Person Completing the Form

Name of person completing this form _____ Date _____

Relationship to patient: ❑ birth, ❑ adoptive, or ❑ foster parent, ❑ caseworker, ❑ medical care provider

❑ other relationship (please specify _____)

Referred by (e.g., who or what organization told you about the clinic ?) _____

Who Should Correspondence be Sent To?

Name _____

Relationship to patient: ❑ birth, ❑ adoptive, or ❑ foster parent ❑ other (specify _____)

Address _____

City _____ County _____ State _____ zip code _____

Telephone Home ( ) _____ Work ( ) _____

Please complete this form to the best of your ability. We realize you will not have the answers to all questions. All information requested in this form is important in allowing us to provide you with the most accurate diagnosis and most appropriate referrals for care. Thank you for taking the time to complete it.

Reasons for Evaluation What are the patient's primary problems? Please be specific.

What do you hope to gain from the evaluation?

Growth

Birth Measures

1. Birth weight: lbs / oz _____ or gms _____

   Birth length: inches _____ or cm _____

   Birth head circumference: inches _____ or cm _____

   Gestational age *(length of pregnancy)*: weeks _____ or months _____

Please provide additional height, weight and head measures if available*

2. Date _____ Weight: lbs _____ or kg _____

   Age _____ Height: inches _____ or cm _____

   Head Circumference: inches _____ or cm _____

3. Date _____ Weight: lbs _____ or kg _____

   Age _____ Height: inches _____ or cm _____

   Head Circumference: inches _____ or cm _____

4. Date _____ Weight: lbs _____ or kg _____

   Age _____ Height: inches _____ or cm _____

   Head Circumference: inches _____ or cm _____

5. Date _____ Weight: lbs _____ or kg _____

   Age _____ Height: inches _____ or cm _____

   Head Circumference: inches _____ or cm _____

Birth Parents' Heights: Birth Mother: inches _____ or cm _____

Birth Father: inches _____ or cm _____

* This information may be available from the patient's physician or school nurse. If growth charts are available and can be photocopied and attached to this form, you need not fill out this section.

Physical Appearance and Health

1. **Photographs of the patient's face are very helpful to us.** The best photos are ones where the face fills the photo and the patient is not smiling. Pictures between ages 1 and 12 years are best.

   - Are such photographs available? ____ yes ____ no
   - Are one or two included with this form? ____ yes ____ no
   - Can others be brought to the clinic? ____ yes ____ no

Please staple photo(s) here:

Photo may be bigger than this space

2. **Was the patient born with (or later discovered to have) any birth defects (things like cleft lip, congenital heart defects, club foot, etc.)?** ____ yes ____ no _____ unknown

   If yes, please describe: _____

   _____

3. **Has this patient ever had:**

	yes	no	unknown		yes	no	unknown
Allergies	_____	_____	_____	Chronic illness of the heart	_____	_____	_____
Multiple ear infections	_____	_____	_____	Chronic illness of the kidneys	_____	_____	_____
Chronic sinusitis	_____	_____	_____	Chronic illness of the joints/limbs	_____	_____	_____
Chronic hearing loss	_____	_____	_____	Chronic illness of the stomach/ bowels	_____	_____	_____
Visual problems	_____	_____	_____				

4. **Has this patient ever had:**

   A. Operations (since birth) ____ yes ____ no ____ unknown

Describe Operation	Surgeon's Name	Patient's Age

   B. Any other hospitalizations ____ yes ____ no ____ unknown

Reason for Hospitalization	Hospital/Doctor	Patient's Age

   C. Physical abuse ____ yes ____ no ____ unknown Age(s): _____

   Was this evaluated by a physician? ____ yes ____ no ____ unknown

   D. Sexual abuse ____ yes ____ no ____ unknown Age(s): _____

   Was this evaluated by a physician? ____ yes ____ no ____ unknown

Neurological Issues

1. Has this patient ever had:

A. Seizures

____ yes ____ no ____ suspected ____ unknown

Type: _____

Age when seizure(s) started: _____

Name(s) of medication(s) given? _____

B. Loss of specific motor skills such as standing, walking, running, etc.

____ yes ____ no ____ unknown

If yes, please describe _____

C. Bed wetting or soiling after 8 years of age.

____ yes ____ no ____ unknown ___ not 8 years old yet

2. Has this patient ever had a head injury leading to unconsciousness or evaluation by a doctor?

____ yes ____ no ____ unknown

If yes, please describe _____

3. Has the patient ever had a CT scan or MRI scan of the brain

____ yes ____ no ____ unknown

If yes, was it described to be abnormal? ____ yes ____ no ____ unknown

Attention Deficit and Hyperactivity

1. Has the patient ever been evaluated for attention deficit/hyperactivity disorder (ADD / ADHD)

____ yes ____ no ____ unknown

If yes:

When was the evaluation done? Age: _____ Date: _____

Was the patient diagnosed with ADD or ADHD? ____ yes ____ no ____ unknown

Was the patient ever treated for ADD or ADHD? ____ yes ____ no ____ unknown

What medications have been tried?

Drug	Dose	Ages	Response

Mental Health Issues

1. Has the patient ever been evaluated by a psychiatrist, psychologist, or MH counselor?

____ yes ____ no ____ unknown

If yes, please list each psychiatrist, psychologist and/or counselor.

A. Type of professional: _____

Reason for assessment: _____

Type of therapy (i.e., behavioral, individual counseling, group counseling, family counseling, medicine): _____

_____

Age at the time of therapy: _____ Did the therapy help? ____ yes ____ no ____ unknown

If yes, how did it help? _____

_____

_____

B. Type of professional: _____

Reason for assessment: _____

Type of therapy (i.e., behavioral, individual counseling, group counseling, family counseling, medicine): _____

_____

Age at the time of therapy: _____ Did the therapy help? ____ yes ____ no ____ unknown

If yes, how did it help? _____

_____

_____

2. Has the patient ever been evaluated for mood problems (depression, anxiety, etc.) or phobia?

____ yes ____ no ____ unknown

If yes:

When was the evaluation(s) done? Age(s): _____ Date(s): _____

3. What medications have ever been tried and how well did they work?

Drug	Dose	Response	Currently Using?

School Issues

1. List ALL schools the patient has attended and the grades of attendance:

School	City	Grades Attended	Received Special Education, Resource Room, Tutoring, etc. yes	no	unknown

2. What learning problems does the patient have?

3. What behavioral problems does the patient have?

Alcohol Exposure

Please fill in this information as completely as possible.
This information is critical to the evaluation of the patient.

Alcohol use by the birth mother

- **Before pregnancy**: average number of drinks per drinking occasion: _____
  maximum number of drinks per occasion: _____
  average number of drinking days per week: _____
  Type(s) of alcohol: ___wine, ___beer, ___ liquor, ___ unknown, ___ other (specify) _____

- **During pregnancy:** average number of drinks per drinking occasion: _____
  maximum number of drinks per occasion: _____
  average number of drinking days per week: _____
  Type(s) of alcohol: ___wine, ___beer, ___ liquor, ___ unknown, ___ other (specify) _____

Which trimester(s) did the mother drink alcohol? ____ 1st ____2nd ____3rd ___unknown

	No	Yes	Unknown
Was the birth mother ever reported to have a problem with alcohol?	____	____	_____
Was the birth mother ever diagnosed with alcoholism?	____	____	_____
Did the birth mother ever receive treatment for alcohol addiction?	____	____	_____

If the above information is unknown, please provide any information that might help describe the mother's level of alcohol use DURING pregnancy _____

_____

_____

What is the source(s) of this information on alcohol use? _____

_____

Did the birth mother use any of the following substances during pregnancy?

Yes	No	Unknown	Type	Please List Specific Substance(s)	Month(s) of Pregnancy
___	___	___	Drugs	_____	_____
___	___	___	Tobacco	_____	_____
___	___	___	Medications	_____	_____
___	___	___	X-rays	_____	_____

Information about the Patient's Biological Parents

Birth mother's name_____ Birth date _____
First Middle Last

Mother's Race ❑ White ❑ Black ❑ American Indian ❑ Alaskan Native ❑ Hispanic
❑ Asian ❑ unknown ❑ other (specify) _____

Education level attained (last year of school completed) _____ Age at birth of patient ____

Does she have a history of learning problems? _____

Birth mother's Address _____
Street City State Zip

When was the last contact with the birth mother? _____

Birth father's name_____ Birth date _____
First Middle Last

Father's Race ❑ White ❑ Black ❑ American Indian ❑ Alaskan Native ❑ Hispanic
❑ Asian ❑ unknown ❑ other (specify) _____

Education level attained (last year of school completed) _____ Age at birth of patient _____

Does he have a history of learning problems? _____

When was the last contact with the birth father? _____

Medical History of the Biological Family

Has anyone in this patient's biological family ever had any of these conditions? *Check all that apply.*

	Birth Mother	Birth Father	Mother's Family	Father's Family	Siblings of patient
Alcoholism					
Birth Defects					
Stillbirths					
Miscarriages					
Mental retardation					
Other developmental disabilities					
Learning disorders					
Attention deficit					
Hyperactivity					
Epilepsy					
Neurological disease					
Child abuse					
Sexual abuse					
Depression					
Suicide					
Mental illness					
Vision problems					
Hearing problems					
Chronic illnesses					
Tourette syndrome					
Delinquency					
Any specific genetic condition					
Other					

Pregnancies of Birth Mother

1. Please list **all** of the birth mother's pregnancies including miscarriages, abortions, in the order of their occurrence:

Year	Length of Pregnancy	First name of child if applicable	Live born Child yes	Live born Child no	Normally Developed yes	Normally Developed no	If not normal, please explain *Include FAS / FAE diagnosis, if known*
_____	_________	___________________	___	___	___	___	_____________________________
_____	_________	___________________	___	___	___	___	_____________________________
_____	_________	___________________	___	___	___	___	_____________________________
_____	_________	___________________	___	___	___	___	_____________________________
_____	_________	___________________	___	___	___	___	_____________________________
_____	_________	___________________	___	___	___	___	_____________________________
_____	_________	___________________	___	___	___	___	_____________________________
_____	_________	___________________	___	___	___	___	_____________________________
_____	_________	___________________	___	___	___	___	_____________________________
_____	_________	___________________	___	___	___	___	_____________________________

Office Use:	Total Parity	Total Gravity	Patient Parity	Patient Gravity	FASD diagnoses

Pregnancy, Labor, and Delivery of this Patient

1. **Did the birth mother experience any difficulties during pregnancy?** __ Yes ___ No ___ Unk.

   If yes, please describe: ____

2. **Did the birth mother receive prenatal care?** ___ Yes ___ No ___ Unknown

3. **Were there complications during the labor or delivery?** ___ Yes ___ No ___ Unknown

   If yes, please explain:____

4. **Was the delivery:** _______ Natural ________ By C-section _______ Unknown

   Reason for C-Section, if performed ____

5. **Where was the patient born?** Hospital___________ City State _________________

6. **Apgar scores** ______________ at 5 minutes _____________ at 10 minutes

7. **How many days did the infant stay in the birth hospital?** _______________________________

8. **Did the patient have any of the following problems while still in the birth hospital?**

	Yes	No	Unknown		Yes	No	Unknown
Feeding problems	____	____	____	Infections	_____	_____	_____
Apnea / breathing difficulties	____	____	____	Jaundice	_____	_____	_____
Supplemental oxygen required	____	____	____	Convulsions	_____	_____	_____

List of Professionals Currently Involved in Patient's Care

Primary Physician Name: _____ Phone: _____

Address: _____

Other Physicians Name: _____ Phone: _____

Specialty: _____

Address: _____

Name: _____ Phone: _____

Specialty: _____

Address: _____

Name: _____ Phone: _____

Specialty: _____

Address: _____

Mental Health Consultants *(includes Psychiatrists Psychologists, and Counselors)* Name: _____ Phone: _____

Specialty: _____

Address: _____

Name: _____ Phone: _____

Specialty: _____

Address: _____

School Name: _____ Phone: _____

Address: _____

Contact Person *(teacher, nurse, counselor, etc.)*:

_____

Other Name: _____ Phone: _____

Profession: _____

Address: _____

Placements

1. List all of the placements the patient has had from birth through today.

Type of placement (i.e., foster, adoptive, etc.)	Duration of placement	Age of patient when placement started
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Office Use:	Total	First	Last

A. How long has the patient been in your care? _____

What to bring to Clinic

If the patient has had any of the following assessments, please bring them to Clinic on the day of your appointment. This information is very important to the patient's diagnostic evaluation.

_____ Facial photographs of the patient from birth to 12 years of age, without a smile.

_____ Medical records which document the problems you have reported above.

_____ School Assessments including:
- Achievement tests
- IQ tests
- Language assessments
- Social Skills assessments
- Behavior assessments

_____ Psychological Assessments

_____ Developmental Assessments including:
- Motor Development (fine and gross motor)
- Occupational Therapy assessments
- Mental (cognitive) assessments

Diagnostic Guide for Fetal Alcohol Spectrum Disorders

The 4-Digit Diagnostic Code™

FASD 4-Digit Code

	3	4	3		4	3	3
Rank 4	severe	all 3 features	abnormal structure/neurology		high	high	high
3	moderate	2.5 features	severe dysfunction		some	some	some
2	mild	1-2 features	moderate dysfunction		unknown	unknown	unknown
1	normal	no features	normal function		none	none	none
	Growth	**Face**	**Brain**		**Prenatal Alcohol**	**Other Prenatal Risks**	**Other Postnatal Risks**

FASD Umbrella

3 Diagnoses under the FASD Umbrella		Growth	FAS Face	Brain		Alcohol
1. FAS	Fetal Alcohol Syndrome	growth	face	severe		exposed
2. SE/AE	Static Encephalopathy / Alc-Exposed			severe		exposed
3. ND/AE	Neurodevelopmental Disorder / Alc-Exposed				moderate	exposed

4th Edition
v.1.01
2024

FAS Diagnostic and Prevention Network
University of Washington
Seattle Washington

This page is purposely blank to support printing the Guide double-sided and bound on the left side. You will also see blank pages occasionally throughout the document allowing new sections to start on the right-hand page with a Tab page placed before it.

We recommend this document be printed in color.

Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code

Fourth Edition
Version 1.01
2024

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FASD4DigitCodeGuide042124.pdf

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Free copies of this Guide can be downloaded from our website:

https://depts.washington.edu/fasdpn/pdfs/Guide2024.pdf

Table of Contents

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March of Dimes Birth Defects Foundation

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I would like to acknowledge the University of Washington FAS Diagnostic & Prevention Network (FASDPN) clinical team members over the past 30 years who have used this Guide weekly and have helped hone the material on an ongoing basis: Special thanks is also extended to our patients and their families who have contributed a wealth of knowledge and information to the ongoing development of this Guide.

Preface

What's New in this 4th Edition, 2024?

The 1st, 2nd and 3rd editions of the Diagnostic Guide were printed in 1997, 1999, and 2004 respectively (Astley and Clarren, 1997, 1999, 2000; Astley 2004). It is now 2024 and a few key updates are warranted for this 4th Edition. These updates are based on our use of the 4-Digit Code for the past 30 years on over 3,000 patients, advancements in medical research, and feedback from over 1,500 clinicians worldwide trained to use the 4-Digit Diagnostic Code. We will continue to make modifications that enhance accuracy, improve clarity, and increase ease of use. We hope you will find this comprehensive approach to the diagnosis of individuals with prenatal alcohol exposure helpful and broadly applicable.

Since the 3rd edition was released in 2004, twenty years of published research has continued to validate the performance of the 2004 guidelines. Selected publications are presented below.

1. Astley SJ, Clarren SK. **(2000)**
   Diagnosing the full spectrum of fetal alcohol exposed individuals: Introducing the 4-Digit Diagnostic Code.

2. Astley SJ. **(2004a)**
   Fetal alcohol syndrome prevention in Washington State: Evidence of success. Video presentation by Susan (Astley) Hemingway in Poland, 2020.

3. Astley SJ, Aylward E, Olson HC, Kerns K, Brooks A, Coggins T, Davies J, Dorn S, Gendler B, Jirikowic T, Kraegel P, Maravilla K, Richards T. **(2009)**
   Magnetic resonance imaging outcomes from a comprehensive magnetic resonance study of children with fetal alcohol spectrum disorders.

4. Astley SJ. **(2011)**
   Canadian palpebral fissure length growth charts reflect a good fit for two school and FASD clinic-based U.S. populations.

5. Astley SJ **(2013)**
   Validation of the fetal alcohol spectrum disorder (FASD) 4-Digit Diagnostic Code.

6. Astley SJ. **(2014)**
   Twenty years of patient surveys confirm a FASD 4-Digit-Code interdisciplinary diagnosis afforded substantial access to interventions that met patients' needs.

7. Astley SJ. **(2015)**
   Palpebral fissure length measurement: Accuracy of the FAS Facial Photographic Analysis Software and Inaccuracy of the Ruler. Pictorial examples comparing the software to the gold standard measure obtained by a sliding digital caliper.

8. Astley SJ, Bledsoe JM, Davies JK. **(2016)**
   The essential role of growth deficiency in the diagnosis of fetal alcohol spectrum disorder.

9. (Astley) Hemingway SJ, Bledsoe JM, Brooks A, Davies JK, Jirikowic T, Olson EM, Thorne JC. **(2019)**
Comparison of the 4-Digit Code, Canadian 2015, Australian 2016 and Hoyme 2016 fetal alcohol spectrum disorder diagnostic guidelines. Link to video for Figure 2C.

10. Kesmodel US, Nygaard SS, Mortensen EL, Bertrand J, Denny C, Glidewell A, (Astley) Hemingway SJ **(2019)**
Are Low-to-Moderate Average Alcohol Consumption and Isolated Episodes of Binge Drinking in Early Pregnancy Associated with Facial Features Related to Fetal Alcohol Syndrome in 5-Year-Old Children?

11. (Astley) Hemingway SJ, Bledsoe JM, Davies JK, Brooks A, Jirikowic T, Olson EM, Thorne JC. **(2019)**
Twin study confirms virtually identical prenatal alcohol exposures can lead to markedly different fetal alcohol spectrum disorder outcomes - fetal genetics influences fetal vulnerability.

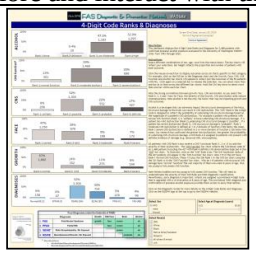
12. (Astley) Hemingway SJ **(2020)**
High facial specificity and positive predictive value are required to diagnose fetal alcohol syndrome when prenatal alcohol exposure is unknown.

13. (Astley) Hemingway SJ, Davies JK, Jirikowic T, Olson EM. **(2020)**
What proportion of the brain structural and functional abnormalities observed among children with fetal alcohol spectrum disorder is explained by their prenatal alcohol exposure and their other prenatal and postnatal risks?

14. (Astley) Hemingway SJ, Baldwin M, Pierce-Bulger M. **(2023)**
Washington and Alaska statewide FASD diagnostic clinical networks: Comparison of three decades of 4-Digit Code diagnostic outcomes and prenatal alcohol exposure histories.

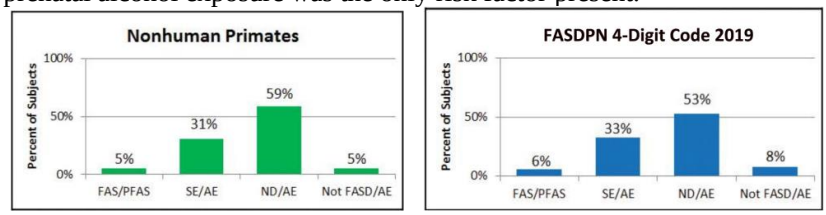
15. Pruner M, Jirikowic T, Baylor C, Hemingway SJA. **(2024)**
Developmental, sensory and behavioral outcomes among infants and toddlers with prenatal alcohol exposure.

16. (Astley) Hemingway SJ. **(1993-2024)**
FASDPN web-based interactive Tableau dashboards allow Users to explore and interact with the FASDPN data. The clinical/research database contains over 2,000 fields of information collected on over 3,000 individuals (newborn to adult) with prenatal alcohol exposure evaluated in the Washington State FASDPN clinics from 1993 through the present. All individuals received an FASD diagnostic evaluation by an interdisciplinary team using the FASD 4-Digit Diagnostic Code.



Research to date continues to confirm:

- **FASD is a spectrum of outcomes, not just severe outcomes** (Astley et al., 2019). The 4-Digit Code is currently the only FASD diagnostic system that includes "moderate" dysfunction (Neurodevelopmental Disorder / Alcohol Exposed (ND/AE)) as well as severe dysfunction (Static Encephalopathy / Alcohol Exposed (SE/AE)) under the umbrella of FASD. Nonhuman primate research confirms that moderate dysfunction (ND/AE) is the most prevalent outcome caused by prenatal alcohol exposure (Clarren et al., 1992). When using the 4-Digit Code, the prevalence of diagnostic outcomes observed in the University of Washington (UW) FASDPN diagnostic clinic matches the prevalence observed in a nonhuman primate model of FASD where prenatal alcohol exposure was the only risk factor present.



- **FASDs are disorders caused by the full continuum of prenatal alcohol exposure (PAE), not just higher exposures.** The higher the exposure the greater the risk, but lower exposures are not risk free (Kesmodel et al., 2019; Astley, 2013). Requiring a threshold level of PAE implies reported levels of PAE are reliably accurate. They are not. When thresholds of exposure are required for diagnosis, over half of individuals with confirmed PAE and severe brain abnormalities do not receive a diagnosis of FASD because details regarding quantity, frequency and timing of exposure are not available. Over half of individuals with the most severe outcome (FAS) have reportedly low to moderate PAE ((Astley) Hemingway, et al., 2019; Petryk et al., 2019). It is also important to note that the teratogenic impact of PAE is not just dependent on the quantity, frequency and timing of exposure. Our twin study confirmed fetal genetics influences fetal vulnerability to PAE ((Astley) Hemingway et al., 2019a). When twin pairs with virtually identical PAE were genetically identical (monozygotic), their FASD diagnoses were identical. When twin pairs with virtually identical PAE were genetically different (dizygotic), close to half (44%) presented with discordant FASD diagnoses. The same level of prenatal alcohol exposure that posed a lower risk for one twin, posed a high risk for the other twin.

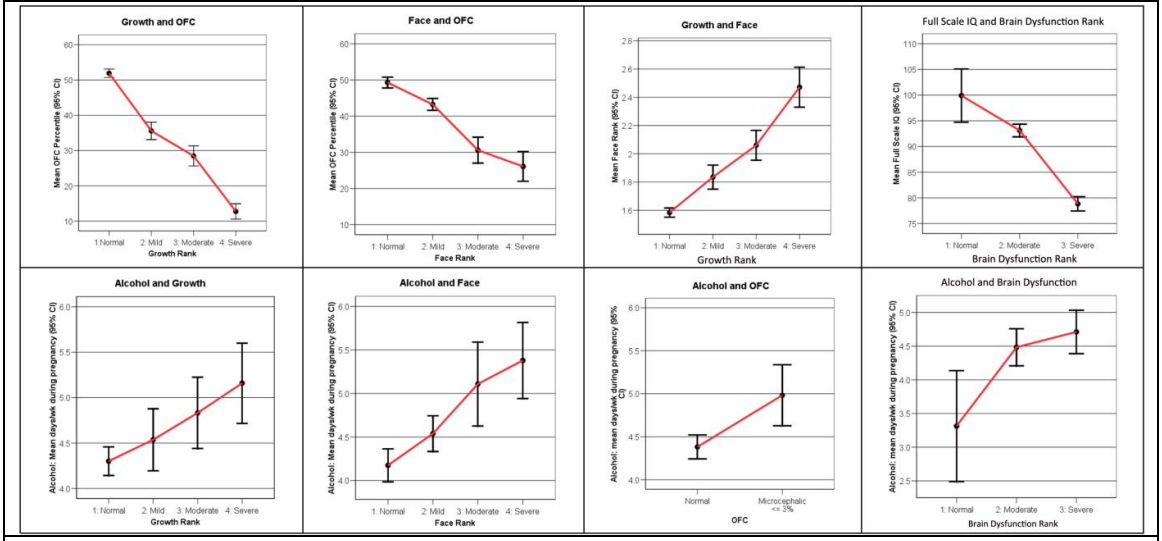
- **FASD is present at birth and can/should be diagnosed at birth to maximize intervention effectiveness** (Pruner et al., 2024; Astley et al., 2019; Astley et al., 2024). Fifteen percent of the patients diagnosed with FASD at the FASDPN over the past 30 years were birth to 3 years of age. Their diagnoses spanned the full continuum of FASD.

- **Growth deficiency (GD) is an essential diagnostic criterion for FASD** (Astley et al., 2016). Based on our empirical study of GD and FASD, GD was significantly correlated with prenatal alcohol exposure. Among individuals with PAE, GD was as prevalent as the other core diagnostic features (facial and brain abnormalities). GD occurred across the full spectrum of FASD diagnoses and increased in prevalence with increasing severity of diagnosis. The most prevalent form of GD was postnatal short stature. GD was as highly correlated with, and predictive of, severe brain dysfunction as the FAS facial phenotype. Individuals with GD had a

two to three-fold increased risk for severe brain dysfunction. Sixty percent of patients with severe GD had severe brain dysfunction. GD accurately predicted which infants had severe brain dysfunction that would not be detectable until later in childhood.

- **The Rank 4 FAS facial phenotype, as defined by the FASD 4-Digit Code, is the only facial phenotype** (Astley et al., 2019) **identified to date that provides sufficient positive predictive value (PPV) and specificity to prenatal alcohol exposure (100%) to allow the facial phenotype to be used as confirmation of prenatal alcohol exposure in a diagnostic setting when a written or verbal documentation of prenatal alcohol exposure is not available** (Astley, et al., 2020). The Rank 4 FAS facial phenotype can also be used to confirm an individual's prenatal alcohol exposure adversely impacted their fetal development. If the facial phenotype of FAS can only be caused by prenatal alcohol exposure, the following two conditions should hold true: 1) All individuals with the FAS facial phenotype have prenatal alcohol exposure (100% PPV); and 2) No individual with a confirmed absence of prenatal alcohol exposure will have the FAS facial phenotype (100% specificity). FASDPN data to date documents the Rank 4 FAS facial phenotype meets these two conditions.

- **FASD is defined by growth deficiency, FAS facial features and brain abnormalities caused by prenatal alcohol exposure (PAE).** If PAE causes FASD, one would expect: 1) strong intercorrelations between the growth, face and brain outcomes among individuals with PAE and 2) strong correlations between each of these three outcomes and prenatal alcohol exposure. This is exactly what is observed when using the 4-Digit Code. The plots below clearly demonstrate growth, face, brain and PAE all present along clinically meaningful continuums; the features are not simply present or absent. (Astley, 2013). The plots also demonstrate that growth, face and brain abnormalities are not only strongly intercorrelated with one another but also increase in severity with increasing PAE. This is powerful evidence supporting a causal association between PAE and these three outcomes.



Significant intercorrelations between growth, face, brain and prenatal alcohol exposure among 3,000 individuals with prenatal alcohol exposure diagnosed with FASD using the FASD 4-Digit Code.

Based on our published studies to date, we recommend the following updates when using this 4th edition of the guidelines (2024):

A. **Updated normal growth charts in electronic format are now widely available on the internet**. We recommend clinicians use the most current electronic charts for height, weight and head circumference that best match the age, sex, race/ethnicity, and country of origin of each patient (See Section III B.2). In our Seattle WA FASDPN clinic, we currently use the CDC, WHO and Rollins et al (2010) growth charts for OFC, weight and height and adjust for mid-parental height (Himes et al., 1985), when both parents' heights are available.

B. **We recommend using the free FAS Facial Photographic Analysis Software (2016, v2.1) distributed by the FASDPN to obtain the most accurate measures of the facial features** (Astley, 2015). The Facial Software incorporates an adjustment factor that is confirmed to accurately measure a palpebral fissure length from a 2-dimensional digital photo within 0.2 mm of the gold standard of measure (a sliding digital caliper). We do not recommend using a handheld ruler to measure PFLs. Numerous studies have confirmed the inaccuracy of the ruler method. We use the Iosub African American PFL charts (Iosub et al., 1985) for individuals that are full or half African American and the Stromland Scandinavian PFL charts for all other races (Stromland. et al., 1999). These charts come with our FAS Facial software and are available in our free excel PFL Z-score calculator. The Hall (1989) Caucasian PFL charts for birth to 16 years are no longer used and should not be used (Astley, 2011; Clarren et al., 2010).

C. **The University of Washington Lip-Philtrum Guides are the only guides that can be validly used to measure the lip and philtrum in accordance with the FASD 4-Digit Code** (Astley et al., 2019). Other Lip/Philtrum Guides may look similar, but are case-defined very differently (e.g., the Rank 4 thin upper lip on the North American Lip/Philtrum Guide (Hoyme et al., 2016) is equivalent to the Rank 2 moderately thick upper lip on the University of Washington Caucasian Lip-Philtrum Guide (Astley et al., 2019). The Seattle FASDPN clinic uses Lip-Philtrum Guide 1 for Caucasians and all races with thinner lips like Caucasians. Lip Philtrum Guide 2 is used for African Americans and all races with thicker lips like African Americans (e.g., Aboriginal Australians).

D. **The 4-Digit Code provides a classification scheme for the full spectrum of FASD and prenatal alcohol exposure that can be used in both the research and clinical arenas**. There are 246 different 4-Digit Codes that range from 1111 (normal development with confirmed absence of prenatal alcohol exposure) to 4444 (full FAS with high prenatal alcohol exposure). These 246 codes can be grouped into 19 different diagnostic categories. Only 108 of the 246 codes fall under the umbrella of FASD. These 108 codes are grouped into 6 distinct FASD diagnostic categories that differentiate individuals with different combinations of growth deficiency, FAS facial features, brain abnormalities and prenatal alcohol exposures. The clinical arena is best served by the smallest number of clinically distinct diagnostic categories that reflect the full spectrum of outcome and exposure. It is for this reason the FASDPN further collapses the 6 Diagnostic Categories for FASD into 3 clinically meaningful subgroups (FAS, SE/AE and ND/AE). FAS includes Diagnostic Category A (see Section IV). SE/AE includes Diagnostic Categories B and C. ND/AE includes Diagnostic Categories D, E and 4 codes in J. The research arena benefits most from a numeric approach to classification (the 4 digits) because the codes

can be used independent of clinical diagnostic nomenclature, can be sorted into any number of subgroups that best meet the study group requirements for the research question at hand and can be used as a universal method for describing FASD study group(s) enrolled across studies. Numeric codes expressed on ordinal scales (e.g., FAS facial phenotype absent, mild, moderate, severe) also provide greater statistical power to identify clinically meaningful correlations between outcomes and exposures than nominal categories expressed on dichotomous scales (e.g., FAS facial phenotype present/absent). Both the clinical and research arenas benefit from a FASD diagnostic system of classification (4-digit numeric codes) that is expressed in the universal language of numbers and portrays, at a glance, the magnitude of expression of each feature (e.g., 4-Digit Code 2334 reflects mild growth deficiency, moderate expression of the FAS facial phenotype, severe brain dysfunction and high prenatal alcohol exposure). Perhaps most importantly, as the clinical arena continues to strive for consensus on how to define and name the clinical subgroups under the umbrella of FASD, the 4-Digit Codes can be collapsed into any number of diagnostic categories The codes can be used independent of the clinical diagnostic names (FAS, SE/AE, ND/AE, ARND, ND-PAE, ARBD) one may apply to the subgroupings of the codes.

E. **The diagnostic term *Neurobehavioral Disorder / Alcohol Exposed* (ND/AE) has been replaced with the term *Neurodevelopmental Disorder / Alcohol Exposed (*ND/AE).** Neurodevelopmental disorders are defined as a group of conditions with onset in the developmental period, inducing deficits that produce impairments of functioning (Morris-Rosendahl & Crocq, 2020). This term is a better fit for the criteria used to define this 4-Digit Code diagnostic category; criteria that remain unchanged in this 4th edition.

F. **Diagnostic Categories A, B and C have been collapsed into a single Category A labeled FAS.** In the 3rd edition (Astley, 2004), Categories A, B and C distinguished *FAS/Alcohol exposed*, *FAS/Alcohol exposure unknown*, and *Partial FAS/Alcohol exposed*, respectively. These three categories have been collapsed into a single Category A labeled FAS for the following reasons. The 4-Digit Codes clearly reflect the various combinations of growth deficiency, FAS facial features, brain abnormalities and prenatal alcohol exposure that meet criteria for FAS. The 4-Digit Code no longer uses the term *Partial FAS* because too often the term was misinterpreted as a milder form of FAS (e.g. had less severe brain dysfunction), potentially jeopardizing an individual's opportunity to qualify for intervention services/supports. The only features that were partially expressed in *Partial FAS* were the growth and/or facial features, not the brain damage. The level of brain damage in Partial FAS was as severe as that required for *FAS*.

G. **Diagnostic Category D: FAS Phenocopy has been removed.** The 4 codes under this category (3431, 3441, 4431, 4441) have been moved to Category N: *Sentinel physical finding(s) / static encephalopathy / no alcohol exposure*. The name applied to Category N is more informative and avoids any potential chart lore confusion that *FAS Phenocopy* is FAS. The growth, face and brain ranks for these 4 codes meet criteria for FAS, but the confirmed absence of prenatal alcohol exposure rules out FAS. These 4-Digit Code outcomes could occur in an individual with growth deficiency and brain dysfunction whose familial facial phenotype happens to match that of FAS. Phenocopies such as these are expected to be rare and to date have never been observed in the FASDPN clinic.

H. **Two 4-Digit Codes (1432 and 1442) were moved from the 2004 Diagnostic Category: *K [sentinel physical finding(s) / static encephalopathy / alcohol exposure unknown*] to the new 2024 Category *A [Fetal alcohol syndrome*].** Since their sentinel physical finding was the Rank 4 FAS facial phenotype and the Rank 4 face provides confirmation of prenatal alcohol exposure when written or verbal evidence of alcohol exposure is unknown (Alcohol Rank 2); these two codes are more appropriately placed in Category A. Among over 4,500 patients evaluated in the FASD diagnostic clinics in AK and WA State (Astley et al, 2024) over 20 and 30 years respectively, only 4 individuals received a diagnosis of 1442. None received a diagnosis of 1432.

I. **Throughout this Guide, weblinks have been inserted** to provide clinicians with easy access to literature citations, diagnostic tools and forms, and training opportunities.

J. Finally, **all diagnostic forms in this Guide are posted on the FASDPN website and have been updated** to reflect this 4th edition of the Guide. The Online Course has also been updated. Those who have already completed the Online Course need not take it again.

FASD 4-Digit Code

Rank	**3** Growth	**4** Face	**3** Brain	**4** Prenatal Alcohol	3 Other Prenatal Risks	3 Other Postnatal Risks
4	severe	all 3 features	abnormal structure/neurology	high	high	high
3	moderate	2.5 features	severe dysfunction	some	some	some
2	mild	1-2 features	moderate dysfunction	unknown	unknown	unknown
1	normal	no features	normal function	none	none	none

FASD Umbrella

3 Diagnoses under the FASD Umbrella		Growth	FAS Face	Brain	Alcohol
1. FAS	Fetal Alcohol Syndrome	growth	face	severe	exposed
2. SE/AE	Static Encephalopathy / Alc-Exposed			severe	exposed
3. ND/AE	Neurodevelopmental Disorder / Alc-Exposed			moderate	exposed

I. Introduction

A. What is Fetal Alcohol Syndrome (FAS) and Fetal Alcohol Spectrum Disorders (FASD)

FAS is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. The definition of the FAS has changed little since the 1970's when the condition was first described and refined at the University of Washington in Seattle WA (Jones and Smith, 1973; Rosett, 1980; Clarren and Smith, 1978; Sokol and Clarren, 1989; Stratton *et al*., 1996). The condition has been broadly characterized by prenatal and/or postnatal growth deficiency, a unique cluster of minor facial anomalies, and brain structural, neurological and/or functional abnormalities. Prenatal alcohol is a leading known cause of intellectual/developmental disabilities in the Western World (Abel & Sokol, 1987) and is preventable. The prevalence of FAS is estimated to be 1 to 3 per 1,000 live births (Stratton et al., 1996) in the general population, but has been documented to be as high as 10 to 15 per 1,000 in some high-risk populations like foster care (Astley et al., 2002).

The physical, cognitive, and behavioral deficits observed among individuals with prenatal alcohol exposure are not dichotomous, that is either normal or clearly abnormal. Rather, the outcomes, and the prenatal alcohol exposure, all range along separate continua from normal to clearly abnormal and distinctive. This full range of outcomes observed among individuals with prenatal alcohol exposure has come to be called Fetal Alcohol Spectrum Disorders (FASD). FASD is a spectrum of disorders **caused** by prenatal alcohol exposure. FAS is the most severe diagnosis under the umbrella of FASD.

Although reference to the harmful effects of prenatal alcohol exposure on infant outcome date back to biblical times, it was not until 1968 when the first reference was published in the medical literature by Lemoine and colleagues from France (Lemoine et al., 1968). Ulleland and colleagues from the United States published similar research findings in 1970 and 1972 (Ulleland et al., 1970; Ulleland, 1972). In 1973, Jones and Smith coined the term FAS (Jones & Smith, 1973) to describe a subset of alcohol-exposed children, obtained from Dr. Ulleland's study and their own clinical records, who shared a common pattern of malformation (Jones et al., 1973).

B. The Diagnostic Challenge

Individuals with prenatal alcohol exposure present with a wide range of outcomes, most of which are not specific to (caused only by) prenatal alcohol exposure and often manifest differently across the lifespan. Professionals from multiple disciplines (medicine, psychology, speech-language pathology, occupational therapy, etc.) are needed to accurately assess and interpret the broad array of outcomes that define the diagnoses. The pattern and severity of outcome is dependent in part on the timing, frequency, and quantity of alcohol exposure (which is rarely known with any level of accuracy) and the fetus' genetic vulnerability to prenatal alcohol exposure (Astley et al., 2019a). The pattern and severity of outcome is also dependent on the other prenatal and postnatal risk factors that are prevalent among individuals with prenatal alcohol exposure (Astley, 2020; Astley et al., 2020).

In the absence of accurate, precise, and unbiased methods for measuring and recording the severity of exposures and outcomes in individual patients, diagnoses have varied widely from clinic to clinic

(Aase, 1994; Astley & Clarren 2000; Chavez et al., 1988; Stratton et al., 1996). From a clinical perspective, diagnostic misclassification leads to inappropriate patient care, increased risk for secondary disabilities (Streissguth & Kanton, 1997) and missed opportunities for primary prevention. From a public health perspective, diagnostic misclassification leads to inaccurate estimates of incidence and prevalence (Stratton et al., 1996). Inaccurate estimates thwart efforts to allocate sufficient social, educational, and health care services to this high-risk population, and preclude accurate assessment of primary prevention intervention efforts. From a clinical research perspective, diagnostic misclassification reduces the power to identify clinically meaningful contrasts between FAS and control groups (Astley & Clarren, 2001). Non-standardized diagnostic methods prevent valid comparisons between studies.

The 4-Digit Diagnostic Code was first released in 1997 (Astley & Clarren, 1997) to address the following limitations in the conventional gestalt approach to diagnosing individuals with prenatal alcohol exposure.

1. *There have been no standardized operational definitions for FAS or for any of the other diagnoses that fall under the umbrella of FASD. Rather, there have been diagnostic guidelines that physicians have been encouraged to follow, but the guidelines have not been sufficiently specific to assure diagnostic accuracy or precision.*

   For example, according to the diagnostic guidelines published by Sokol and Clarren (1989), which were a minor modification of the 1980 definition of FAS by the Fetal Alcohol Study Group of the Research Society for Alcoholism (Rosett, 1980), which, in turn, were derived from the work of Clarren and Smith (1978): "The diagnosis of FAS can only be made when the patient has signs of abnormality in each of the three categories: 1) Prenatal and/or postnatal growth retardation [weight and/or length below the 10th percentile when corrected for gestational age], 2) central nervous system involvement (including neurological abnormality, developmental delay, behavioral dysfunction or deficit, intellectual impairment, and/or structural abnormalities, such as microcephaly [head circumference below the 3rd percentile or brain malformations found on imaging studies or autopsy] and 3) a characteristic face, currently qualitatively described as including short palpebral fissures, an elongated midface, a long and flattened philtrum, thin upper lip, and flattened maxilla."

   The 1996 guidelines for the diagnosis of FAS proposed by the Institute of Medicine (Stratton et al., 1996) took a similar approach. The diagnosis of FAS can be made when the patient presents with: "1) Evidence of growth retardation, as in at least one of the following: a) low birth weight for gestational age; b) decelerating weight over time not due to nutrition; or c) disproportional low weight to height; 2) Evidence of a characteristic pattern of facial anomalies that includes features such as short palpebral fissures and abnormalities in the premaxillary zone (e.g., flat upper lip, flattened philtrum, and flat midface); and 3) Evidence of brain neurodevelopmental abnormalities, as in at least one of the following: a) decreased cranial size at birth; b) structural brain abnormalities (e.g., microcephaly, partial or complete agenesis of the corpus callosum, cerebellar hypoplasia);c) neurological hard or soft signs (as age appropriate), such as impaired fine motor skills, neurosensory hearing loss, poor tandem gait, poor eye-hand coordination."

   Although these descriptions do provide guidance, they are not sufficiently specific to assure diagnostic accuracy and precision. They reflect a more "gestalt" approach to diagnosis. The guidelines for brain abnormalities do not address how many areas of deficit must be present, how

severe the deficits must be, or what level of documentation must exist to substantiate the presence of the deficit. The guidelines for the facial phenotype are equally nonspecific. How many facial features must be present, how severe must the features be, and what scale of measurement should be used to judge the severity? One need only read the clinical literature or review medical records, birth certificates, birth defect registries or ICD-9 codes to see how variably these criteria are interpreted, applied and reported (CDC, 1995, 1995a; Cordero et al., 1994; Ernhart et al., 1995; Stratton et al., 1996).

2. *There has been a lack of objective, quantitative scales to measure and report the magnitude of expression of key diagnostic features.*

   For example, although a thin upper lip and smooth philtrum are key diagnostic features (Astley & Clarren, 1996; Clarren & Smith, 1978; Jones & Smith, 1973; Smith, 1979; Stratton et al., 1996), prior to 1997, quantitative measurement scales were never used to measure thinness or smoothness, and guidelines had never been established for how thin or smooth the features must be. Objective quantitative scales not only improve accuracy and precision, but also establish a common numeric language for communicating outcomes in medical records and in the medical literature.

3. *The term fetal alcohol effects (FAE) was broadly used and poorly defined.*

   The term 'suspected fetal alcohol effects' was first introduced into the medical literature in 1978 and was defined as 'less complete partial expressions' of FAS in individuals with prenatal alcohol exposure (Clarren & Smith, 1978). Based on this definition, an individual whose mother drank a few glasses of wine intermittently throughout pregnancy and presented with attention deficit hyperactivity disorder would meet the criteria for FAE. So would an individual whose mother drank a fifth of vodka daily throughout pregnancy and presented with microcephaly, severe intellectual disability, growth deficiency and no facial anomalies. The broad use of this term and the reluctance to abandon it points to the clear need to develop diagnostic terms for individuals with prenatal alcohol exposure who present with physical anomalies and/or cognitive/behavioral disabilities, but do not meet the criteria for FAS. New diagnostic terms that more finely differentiate the variable exposures and outcomes of individual patients, without implying alcohol as the sole causal agent, were needed.

4. *Clinical terms like FAE* (Aase et al., 1995), *alcohol-related birth defects (ARBD) (Stratton et al., 1996,) alcohol-related neurodevelopmental disorder (ARND) (Stratton et al., 1996, Hoyme et al.,2016) and FASD without the Face (Cook et al., 2015) imply a causal link between alcohol exposure and outcome in an individual that, to date, cannot be medically confirmed. As far back as 1995, leading dysmorphologists in the field of FAS diagnosis formally requested that the term FAE no longer be used for this reason (Aase et al., 1995; Sokol & Clarren, 1989).*

   With the exception of the Rank 4 full facial phenotype of FAS, no other physical anomalies or cognitive/behavioral disabilities observed in an individual with prenatal alcohol exposure are necessarily specific to (caused only by) their prenatal alcohol exposure (Stratton et al., 1996). Features such as microcephaly, neurological abnormalities, attention deficit, intellectual disability, and growth deficiency frequently occur in individuals with prenatal alcohol exposure, and frequently occur in individuals with no prenatal alcohol exposure. The diagnostic terms

ARBD, ARND (Hoyme et al., 2016) and FASD without Sentinel Facial Features (Cook et al., 2015) introduce the same limitation as does FAE, namely, implying alcohol exposure caused the birth defect or neurodevelopmental disorder in an individual patient. The 4-Digit Code avoids this problem by using a nomenclature that reports the patient was *exposed* to prenatal alcohol rather than reporting the patient's outcomes are *alcohol effects* or *alcohol-related outcomes*. The 4-Digit Code also requires that all other adverse prenatal and postnatal risks be documented and ranked for they too serve as important risk factors that must be taken into consideration when deriving a diagnosis and intervention plan.

5. *Too often diagnoses depicting FASD are reported in the medical records and medical literature with no documentation of the method used to derive the diagnosis and little or no documentation of the data used to support the diagnosis.*

   Failure to report this information can limit the patient's ability to qualify for and receive appropriate intervention services from subsequent health care, social service, and educational providers. For example, simply reporting that an individual has FAS does little to convey the individual's strengths and disabilities. Some individuals with FAS have low IQs, some have normal IQs, some have attention deficits, some do not, some have challenges with memory, while others have language deficits. From a public health perspective, failure to report these data also prevents surveillance efforts from accurately tracking the prevalence of FASD diagnoses in the population. Suportine data are needed to validate the diagnoses. Accurate surveillance is vital for setting public health policy and assessing the effectiveness of primary prevention efforts. The 4-Digit Code requires data be collected not just to corroborate the diagnosis, but to derive the diagnosis. The 4-Digit Code provides a comprehensive FASD Diagnostic Form for recording all supportive data and provides a numeric classification scheme that is readily incorporated into clinical, research, and surveillance databases.

C. Meeting the Diagnostic Challenge

Each of the above limitations has been largely overcome with the development of the "*4-Digit Diagnostic Code*". The four digits reflect the magnitude of expression of four key diagnostic features of FASD in the following order: (1) growth deficiency, (2) the FAS facial phenotype, (3) brain abnormalities, and (4) prenatal alcohol exposure. The magnitude of expression of each feature is ranked independently on a 4-point Likert scale with 1 reflecting complete absence of the FAS feature and 4 reflecting a strong "classic" presence of the FAS feature. Thus, the 4-Digit Code 4444 reflects the most severe expression of FAS (significant growth deficiency, all three FAS facial features, structural/neurological evidence of brain damage, and confirmed prenatal exposure to alcohol). At the opposite end of the scale is the 4-Digit Code 1111 reflecting normal growth, none of the three FAS facial features, no evidence of brain abnormalities, and confirmed absence of prenatal alcohol exposure. Every combination of 4-Digit Code has been observed among individuals with prenatal alcohol exposure evaluated in the WA State FAS Diagnostic & Prevention Network.

This diagnostic method was developed through the combined expertise of the University of Washington FAS Diagnostic and Prevention Network (FASDPN) interdisciplinary clinical teams (Clarren & Astley, 1997; Clarren et al., 2000) and the comprehensive records of over 3,000 patients (newborn to adult) with prenatal alcohol exposure diagnosed over 30 years at the FASDPN clinics.

D. Benefits of the 4-Digit Diagnostic Code

The 4-Digit Diagnostic Code:

1. Greatly increases diagnostic precision and accuracy through use of objective, quantitative measurement scales, image analysis software, and specific case definitions.

2. Diagnoses the full spectrum of outcomes (FASD) observed in individuals across all ages and all levels of prenatal alcohol exposure.

3. Offers an intuitively logical 4-digit numeric approach to reporting outcomes and exposure that clearly and objectively reflect the magnitude of growth deficiency, FAS facial phenotype, brain abnormality and prenatal alcohol exposure.

4. Documents the presence of prenatal alcohol exposure without implying a causal role.

5. Documents all other prenatal and postnatal adverse exposures and events that can also adversely impact outcome.

6. Most importantly, as the clinical and research fields of FASD strives to achieve consensus on diagnostic criteria and nomenclature worldwide, these 4-Digit Codes are expressed in the universal language of numbers and can be grouped and regrouped into any number of diagnostic categories under the umbrella of FASD and assigned any number of diagnostic names that best meet the widely varying medical systems of care worldwide (Appendix 1).

7. Can be taught to a wide array of health care and social service providers, thus greatly expanding the availability of diagnostic services. (Appendix 1)

The 4-Digit Code currently serves as the cornerstone of a fully integrated and highly successful screening, diagnostic, prevention and surveillance program in Washington State (Astley et al., 2002; Astley, 2004a, 2024; Hemingway (Astley) et al., 2024).

While this document might at first appear complex, clinicians that have used it find this diagnostic approach logical and easy to use, facilitating the proper description and classification of patients presenting along the full spectrum of adverse outcomes and prenatal alcohol exposures.

E. Other Syndromes

The methods of diagnosing FAS arise from the larger fields of teratology and dysmorphology (clinical genetics). It is essential to remember that many birth defect syndromes share *isolated* features, but each is differentiated by a unique *constellation* of features. A few examples of conditions that share some, but not all, of the features of FAS include fetal hydantoin syndrome, maternal PKU fetal effects, and fetal valproate syndrome. It is important to note that alcohol is a teratogen that can adversely impact the development of all fetuses, including fetuses with other syndromes. It is not appropriate to rule-out all other syndromes before rendering a diagnosis of FAS/D. And when rendering a diagnosis of FASD, alternate or co-existing syndromic, medical or psychiatric conditions should be considered at all times.

II. FASD Diagnostic Form

The FASD Diagnostic Form guides the interdisciplinary clinical team in the collection, recording, and interpretation of all key information used to derive accurate and precise diagnoses across the full spectrum of outcomes. All forms presented in this Diagnostic Guide are also available free in electronic format on the FASDPN website. Comprehensive assessments lead to accurate diagnoses and informed intervention plans. Although space has been provided to record a full complement of data, we are not implying all these assessments must be conducted to derive a diagnosis. It is the responsibility of the clinical team to select the most appropriate assessment battery for each patient.

The form also serves as a centralized data repository for efficient generation of the final medical report and is designed to facilitate data entry into a database.

Where is the Information for the Diagnostic Form Obtained?

The information recorded in the FASD Diagnostic Form is obtained from four primary sources:

1. The New Patient Information Form, completed by the caregivers prior to the diagnostic evaluation (Appendix 2), serves as a clinical intake form.

2. Medical/psychological/educational assessments conducted prior to the diagnostic evaluation.

3. Assessments administered by the clinical team at the time of the diagnostic evaluation.

4. The caregiver/patient interview conducted at the time of the diagnostic evaluation

When is the Form Completed and by Who?

Diagnosis of fetal alcohol spectrum disorders by an interdisciplinary team of professionals (medical doctor, psychologist, speech-language pathologist, occupation therapist) will result in the most accurate assessment and interpretation of the broad array of outcomes (growth deficiency, facial anomalies, and structural/neurological/functional brain abnormalities) that define the diagnoses. The FASD Diagnostic Form is completed by the clinical team before and during the patient's clinic visit. Typically, the physician completes the sections pertaining to growth, structural and neurological measures of the brain, facial features and other physical findings. The occupational therapist, psychologist, speech language pathologist, complete the sections pertaining to psychometric measures of brain function. All team members participate in the derivation of the 4-Digit Code and intervention plan.

FASD 4-Digit Code Diagnostic Short Form

A 1-page FASD 4-Digit Code Short Form is available free in electronic format for clinics that choose to record only the data needed to support the patient's 4-Digit Code.

FASD 4-Digit Code Diagnostic Form

Medical #		Clinic		Clinic Date	
Patient's Name	First	MI	Last	Age (y)	Birth date

Person accompanying patient	Name:	Relation:
Relationship(s) to patient	Name:	Relation:

Patient's Race(s)	
Patient's sex at birth:	
Patient's gender identity	
Form completed by:	
Diagnosis made by:	
Diagnosis	

4-Digit Diagnostic Code Grid

(See instructions in Diagnostic Guide for FASD)

FASD 4-Digit Code

Rank	Growth	Face	Brain	Prenatal Alcohol	Other Prenatal Risks	Other Postnatal Risks
4	severe	all 3 features	abnormal structure/neurology	high	high	high
3	moderate	2.5 features	severe dysfunction	some	some	some
2	mild	1-2 features	moderate dysfunction	unknown	unknown	unknown
1	normal	no features	normal function	none	none	none

GROWTH

Prenatal Growth

	Gestational Age	Birth Length			Birth Weight		
Date	(wks)	(cm)	(inches)	(percentile)	(gm)	(lbs/oz)	(percentile)

Postnatal Growth

		Height					Weight		
Date	Age (yrs/months)	(cm)	(inches)	Unadjusted (percentile)	Mid-birthparent Adjustment (cm)	Parent-Adjusted (percentile)	(kg)	(lbs)	(percentile)

Birth Parent's Heights

Birth Mother Height		Birth Father Height		Mid-Parent Height
cm	inches	cm	inches	cm

ABC-Score for Growth Deficiency

See instructions in the "Diagnostic Guide for FASD" for deriving the ABC-score for growth and translating it into a 4-Digit Diagnostic Code

	Circle the ABC Scores for: Height	Weight
≤ 3rd percentile = **C**	C	C
>3rd and ≤ 10th percentile = **B**	B	B
> 10th percentile = **A**	A	A

This ABC Score reflects the patient's growth between _____ years and _____ years of age.

FACIAL FEATURES (and other physical findings)

CURRENT PHENOTYPE Age _____ years Date _____/_____/_____

Direct Measures by Hand

	mm	z-score	Normal Chart Used
Left PFL			
Right PFL			
Mean PFL			
Inner Canthal Distance			

	5-Point Rank	UW Lip-Philtrum Guide Used
Philtrum		
Upper Lip		

2D Photograph or 3D Image

Frontal digital photo filename	Internal measure of scale (dot on forehead)		
	True dot size	Units (mm, cm, inches)	Dot size in photo, pixels

	Length in photo (pixels)	mm	z-score	Normal Chart Used
Left PFL				
Right PFL				
Mean PFL				
Inner Canthal Distance				

Photo filename		5-Point Rank	UW Lip-Philtrum Guide	
	Philtrum			Upper Lip Circularity
	Upper Lip			

PAST PHENOTYPE Age _____ years Date _____/_____/_____

Source of Information	Internal measure of scale (dot on forehead)		
	True dot size	Units (mm, cm, inches)	Dot size in photo (pixels)
Photo:			
Text Record:			

	Length in photo (pixel)	mm	z-score	Normal Chart Used
Left PFL				
Right PFL				
Mean PFL				
Inner Canthal Distance				

Photo filename		5-Point Rank	UW Lip-Philtrum Guide	
	Philtrum			Upper Lip Circularity
	Upper Lip			

FACIAL ABC-SCORE *See instructions in the "Diagnostic Guide for FASD" for deriving the ABC Score and 4-Digit Code*

5-Point Likert Rank for Philtrum & Lip	Z-score for Palpebral Fissure Length	*Circle the ABC Scores for:* Palpebral Fissure	Philtrum	Upper Lip
4 or 5	≤ -2 SD	C	C	C
3	>-2 SD and ≤ -1 SD	B	B	B
1 or 2	> -1 SD	A	A	A
Source of Data for each Facial Feature ➜				

OTHER PHYSICAL FINDINGS / ANOMALIES / SYNDROMES / MEDICAL CONDITIONS

BRAIN

Severity Score: Severity of Delay/Impairment (Displayed along left margin)
Circle: **0** = Unknown, Not Assessed **1** = Within Normal Limits **2** = Mild to Moderate **3** = Severe

Severity **STRUCTURAL**

0 1 2 3 OFC	cm	smallest %tile	date	cm	%tile	date	cm	%tile	date

0 1 2 3 Structural anomalies seen on brain imaging: _____
0 1 2 3 Other: _____

NEUROLOGICAL

0 1 2 3 Seizures: type: _____ meds._____ Date of onset _____
0 1 2 3 Other neurological signs (vision, hearing, tics, tremors):_____
_____

FUNCTIONAL/Standardized Measures *Document most recent, valid test scores.*

0 1 2 3 **Cognition** (e.g., WISC, WAIS, DAS, TONI, Stanford-Binet, etc.)

0 1 2 3 **Processing Speed** (e.g., WISC, etc.)

Other Test/Subtest Names	*Score*	*Type of Score*	*Date*	*Other Test/Subtest Names*	*Score*	*Type of Score*	*Date*

0 1 2 3 **Academic Achievement** (e.g., WIAT, Woodcock Johnson, WRAT, Keymath, etc.)

Test/Subtest Name	*Score*	*Type of Score*	*Date*	*Test/Subtest Name*	*Score*	*Type of Score*	*Date*

0 1 2 3 **Adaptive Behavior / Social Skills** (e.g., VABS, BASC, ABAS, etc.)

Test/Subtest Name	*Score*	*Type of Score*	*Date*	*Test/Subtest Name*	*Score*	*Type of Score*	*Date*

BRAIN (Continued)

Severity Score: Severity of Delay/Impairment (Displayed along left margin)
Circle: **0** = Unknown, Not Assessed **1** = Within Normal Limits **2** = Mild to Moderate **3** = Severe

Severity

0 1 2 3 **Executive Function** (e.g., D-KEFS, Rey Complex Figure Test, WCST, NEPSY, etc.)

Test/Subtest Name	*Score*	*Type of Score*	*Date*	*Test/Subtest Name*	*Score*	*Type of Score*	*Date*

0 1 2 3 **Memory** (CVLT, WRAML, Rey Complex Figure Test, etc)

Test/Subtest Name	*Score*	*Type of Score*	*Date*	*Test/Subtest Name*	*Score*	*Type of Score*	*Date*

0 1 2 3 **Motor** (e.g., PDMS, QNST, VMI, Brunuinks-Oseretsky Scales of Motor Dev, etc.)

0 1 2 3 **Sensory** (e.g., SSP, AASP, etc.)

Test/Subtest Name	*Score*	*Type of Score*	*Date*	*Test/Subtest Name*	*Score*	*Type of Score*	*Date*

0 1 2 3 **Language** (e.g., TOLD, PLS, CELF, TOWL etc.)

0 1 2 3 **Social Communication** (e.g., SCQ etc.)

0 1 2 3 **Speech Articulation** (Arizona, etc.)

Test/Subtest Name	*Score*	*Type of Score*	*Date*	*Test/Subtest Name*	*Score*	*Type of Score*	*Date*

BRAIN (Continued)

Severity Score: Severity of Delay/Impairment (Displayed along left margin)
Circle: **0** = Unknown, Not Assessed **1** = Within Normal Limits **2** = Mild to Moderate **3** = Severe

Severity

0 1 2 3 **Mental Health/Psychiatric Conditions:** (e.g., ADHD, ODD, Maj. Depression, ASD, etc)

Disorder	*Date Diagnosed*	*Disorder*	*Date Diagnosed*	*Disorder*	*Date Diagnosed*

Medication. √ if Currently Taking	*Response (+, -, none)*	*Medication. √ if Currently Taking*	*Response (+, -, none)*	*Medication. √ if Currently Taking*	*Response (+, -, none)*

0 1 2 3 **Behavior/Attention/Activity Level** (e.g., CBCL, Conners Rating Scale, NICHQ, BASC, CSHQ, etc.)

Test/Subtest Name	*Score*	*Type of Score*	*Date*	*Test/Subtest Name*	*Score*	*Type of Score*	*Date*

0 1 2 3 **Development** (e.g., Bayley Scales of Infant Dev., Battelle Dev. Invent., Miller Assessment of Preschoolers, etc.)

Test/Subtest Name	*Score*	*Type of Score*	*Date*	*Test/Subtest Name*	*Score*	*Type of Score*	*Date*

BRAIN (Continued)

FUNCTIONAL / Non-Standardized Observational Measures

Severity Score: Severity of Delay/Impairment (Displayed along left margin)
Circle: **0** = Unknown, Not Assessed, Too Young **1** = Within Normal Limits **2** = Mild to Moderate **3** = Severe

Severity **Caregiver Interview**

Planning / Temporal Skills

0 1 2 3 Needs considerable help organizing daily tasks _____
0 1 2 3 Can not organize time _____
0 1 2 3 Does not understand concept of time _____
0 1 2 3 Difficulty in carrying out multi-step tasks _____
0 1 2 3 Other _____

Behavioral Regulation/ Sensory Motor Integration

0 1 2 3 Poor management of anger / tantrums _____
0 1 2 3 Mood swings _____
0 1 2 3 Impulsive _____
0 1 2 3 Compulsive _____
0 1 2 3 Perseverative _____
0 1 2 3 Inattentive _____
0 1 2 3 Inappropriately [high or low] activity level _____
0 1 2 3 Lying/stealing _____
0 1 2 3 Unusual [high or low] reactivity to [sound touch light] _____
0 1 2 3 Other _____

Abstract Thinking / Judgment

0 1 2 3 Poor judgment _____
0 1 2 3 Cannot be left alone _____
0 1 2 3 Concrete, unable to think abstractly _____
0 1 2 3 Other _____

Memory / Learning / Information Processing

0 1 2 3 Poor memory, inconsistent retrieval of learned information _____
0 1 2 3 Slow to learn new skills _____
0 1 2 3 Does not seem to learn from past experiences _____
0 1 2 3 Problems recognizing consequences of actions _____
0 1 2 3 Problems with information processing speed and accuracy _____
0 1 2 3 Other _____

Spatial Skills and Spatial Memory

0 1 2 3 Gets lost easily, has difficulty navigating from point A to point B _____
0 1 2 3 Other _____

Social Skills and Adaptive Behavior

0 1 2 3 Behaves at a level notably younger than chronological age _____
0 1 2 3 Poor social/adaptive skills _____
0 1 2 3 Other _____

Motor/Oral Motor Control

0 1 2 3 Poor/delayed motor skills _____
0 1 2 3 Poor balance _____
0 1 2 3 Other _____

BRAIN (Continued)

FUNCTIONAL DOMAINS

Examples include, but are not limited to Memory, Cognition, Language, Executive Function, Motor, and Attention.

Severity Score: Severity of Delay/Impairment (Displayed along left margin)
Circle: **0** = Unknown, Not Assessed **1** = Within Normal Limits **2** = Mild to Moderate **3** = Severe

Severity		
0 1 2 3	Name of Domain	
	Supportive Evidence	
0 1 2 3	Name of Domain	
	Supportive Evidence	
0 1 2 3	Name of Domain	
	Supportive Evidence	
0 1 2 3	Name of Domain	
	Supportive Evidence	
0 1 2 3	Name of Domain	
	Supportive Evidence	
0 1 2 3	Name of Domain	
	Supportive Evidence	
0 1 2 3	Name of Domain	
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0 1 2 3	Name of Domain	
	Supportive Evidence	
0 1 2 3	Name of Domain	
	Supportive Evidence	
0 1 2 3	Name of Domain	
	Supportive Evidence	
0 1 2 3	Name of Domain	
	Supportive Evidence	
0 1 2 3	Name of Domain	
	Supportive Evidence	

MATERNAL ALCOHOL USE

Alcohol Consumption of the Birth Mother

Before Pregnancy	**average number of drinks** per drinking occasion:					
	maximum number of drinks per occasion:					
	average number of **drinking days per week**:					
	Type(s) of alcohol	wine	beer	liquor	unknown	Other (specify)

During Pregnancy	**average number of drinks** per drinking occasion:					
	maximum number of drinks per occasion:					
	average number of **drinking days per week**:					
	Type(s) of alcohol	wine	beer	liquor	unknown	Other (specify)

Trimester(s) in which alcohol was consumed	1st	2nd	3rd	unknown	none
Was the birth mother ever reported to have a **problem** with alcohol?	yes	suspected	no	unknown	
Was the birth mother ever **diagnosed** with alcoholism?	yes	suspected	no	unknown	
Did the birth mother ever **receive treatment** for alcohol addiction?	yes	suspected	no	unknown	
Was alcohol use during this pregnancy **positively confirmed** through verbal or written documentation?	yes	no			
If yes, **source** of verbal or written confirmation:					
Reported use of alcohol during this pregnancy is:	Reliable	Somewhat reliable		Unk. reliability	
Was the Rank 4 FAS facial phenotype used as a proxy measure of prenatal alcohol exposure?	yes	no			
Other information about alcohol use **during this pregnancy**					

4-DIGIT RANK for Alcohol Exposure

4-Digit Diagnostic Rank	Prenatal Alcohol Exposure Category	Description
4	High Risk	● Alcohol use during pregnancy is CONFIRMED. *and* ● Reported exposure pattern is consistent with the medical literature placing the fetus at "high risk" (generally high peak blood alcohol concentrations delivered at least weekly in early pregnancy, reports of intoxication, binge-drinking).
3	Some Risk	● Alcohol use during pregnancy is CONFIRMED. *and* ● Level of alcohol use is reported to be less than in Rank (4) or the level is unknown.
2	Unknown Risk	● Alcohol use during pregnancy is UNKNOWN (cannot be confirmed or ruled-out).
1	No Risk	● Alcohol use during pregnancy is CONFIRMED to be completely ABSENT from conception to birth.

Circle the 4-Digit Diagnostic Rank in the table above that best reflects the patient's Prenatal Alcohol Exposure

OTHER PRENATAL AND POSTNATAL RISK FACTORS

PRENATAL RISKS:

No known risk	Unknown risk	Some risk	High risk
1	2	3	4

See the "Diagnostic Guide for FASD" for instructions on deriving the rank for Other Prenatal Risks.

Prenatal:

1. Parity ____, Gravity ____ of this birth. Birth order if child is the result of a multiple birth pregnancy: _____ of _____
2. Prenatal care: ____ Yes, (If yes, when did it start?_____), ___ No, ___ Unknown
3. Complications (specify) _____

Genetics

1. Biological parents learning difficulties

   Mother ___ Yes ____ Suspected __ No __ Unknown. **Father** ___ Yes ____ Suspected ____ No ____ Unknown
2. Other conditions of heritability (ADHD, mental health, syndromes, etc.) that may be relevant to this case. *(specify)*

   _____

Prenatal Exposure to Other Substances (e.g., medications, tobacco, illicit drugs, other teratogens, etc.)

POSTNATAL RISKS:

No known risk	Unknown risk	Some risk	High risk
1	2	3	4

See the "Diagnostic Guide for FASD" for instructions on deriving the rank for Postnatal Risks.

Perinatal Difficulties (prematurity, extended stay in birth hospital, etc.): _____

_____

Medical Conditions: _____

_____

Postnatal Adversity (ACES, TESI, etc):

1. Number of out-of-home placements _____ Age at first out-of-home placement _____ Age at last placement _____
2. Please report the age range for all adversities experienced by the patient. If age is unknown, enter Yes, No Suspected or Unknown in each box.

Adversity	age range	Adversity	age range	Adversity	age range
sexual abuse		orphanage/group care		serious medical issue	
physical abuse		abandonment		substance abuse (patient)	
emotional abuse		homelessness		patient incarceration	
domestic violence		poverty		patient suicide attempt	
physical neglect		food insecurity		natural disaster	
emotional neglect		bullying		war, terrorism	
medical neglect		school violence		List others below	
family death		community violence			
family incarceration		discrimination			
parent separated/divorced		serious accident			
family mental health		home fire			
parent substance abuse		animal attack			

Additional details that may be relevant:

FASD 4-Digit Diagnostic Code – Short Form 2024

In lieu of using the 9-page comprehensive Diagnostic Form presented above, this 1-page Short Form documents all pertinent information needed to derive/support the patient's 4-Digit Code. An electronic version of the form is available on the FASDPN website.

FASD 4-Digit Diagnostic Code – Short Form (2024)

*(Astley) Hemingway SJ, Diagnostic Guide for FASD: The 4-Digit Code, 4th ed. 2024

Patient Name		Birth date	
Sex/Gender		Clinic Date	
Race		Age (yrs)	
Clinic Name		Medical #	

NAME OF DIAGNOSIS

FASD 4-DIGIT DIAGNOSTIC CODE

Rank	Growth	Face	Brain	Prenatal Alcohol	Other Prenatal Risks	Other Postnatal Risks
4	severe	all 3 features	abnormal structure/neurology	high	high	high
3	moderate	2.5 features	severe dysfunction	some	some	some
2	mild	1-2 features	moderate dysfunction	unknown	unknown	unknown
1	normal	no features	normal function	none	none	none

DATA BELOW WAS USED TO DERIVE / SUPPORT 4-DIGIT CODE

GROWTH

Date	Height measure	Height percentile	Weight measure	Weight percentile

GROWTH TABLES (Circle ABC Scores to Derive Rank)

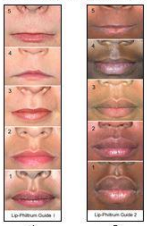
Percentile Range	ABC-Scores for: Height	Weight
≤ 3rd	C	C
> 3rd and ≤ 10th	B	B
> 10th	A	A

4-Digit Diagnostic Rank	Growth Deficiency Category	Height-Weight ABC-Score Combinations
4	Severe	CC
3	Moderate	CB, BC, CA, AC
2	Mild	BA, BB, AB
1	None	AA

FACE

Date		
Right PFL: mm / Z-score		
Left PFL: mm / Z-score		
mean PFL: mm / Z-score		
Philtrum Rank		
Lip Rank		
Lip Circularity		

Circle Guide(s) Used



1 2

FACE TABLES (Circle ABC-Scores to Derive Rank)

5-Point Rank for Philtrum or Lip	Z-scores for Palpebral Fissure Length (PFL)	ABC-Scores for: Palpebral Fissure	Philtrum	Upper Lip
4 or 5	≤ - 2 SD	C	C	C
3	> -2 SD and ≤ -1 SD	B	B	B
1 or 2	> -1 SD	A	A	A

4-Digit Diagnostic Rank	Level of Expression of FAS Facial Features	Palpebral Fissure – Philtrum – Lip ABC-Score Combinations
4	Severe	CCC
3	Moderate	CCB, CBC, BCC
2	Mild	CCA, CAC, CBB, CBA, CAB, CAA BCB, BCA, BBC, BAC ACC, ACB, ACA, ABC, AAC
1	None	BBB, BBA, BAB, BAA ABB, ABA, AAB, AAA

CNS

Rank 4 *Check 1 or more*	☐ microcephaly	☐ abnormal structural brain image	☐ seizure disorder	☐ No evidence			
	Other (specify):						
Rank 2 or 3 *Evidence of Dysfunction*		Domain / Test / Subtest Name			Score (units)		Date
	1						
	2						
	3						

PRENATAL ALCOHOL

	Trimester(s):		Ave. drinking days/week:		Ave. drinks / per occasion:
Other (Specify):					

Other Prenatal and Postnatal Exposures / Events

Risk Rank: (None = 1, Unknown = 2, Some = 3, High = 4)	Prenatal Rank:		Postnatal Rank:	

FASD-4digit-shortform-032024.docx © (Astley) Hemingway-University of Washington, Seattle, WA Page 1 of 1

III. Instructions for Deriving the 4-Digit Code

A. The 4-Digit Diagnostic Code

What are the 4 Digits?

The four digits reflect the magnitude of expression of the four key diagnostic features of FASD in the following order: (1) growth deficiency, (2) the FAS facial phenotype, (3) brain abnormalities, and (4) prenatal alcohol exposure. Individuals with prenatal alcohol exposure often present with a myriad of other prenatal and postnatal risks that could also adversely impact growth and development. These too are documented. The 4-Digit Diagnostic Code is generated at the completion of the diagnostic evaluation using information recorded on the FASD Diagnostic Form. The code is derived following the directions in Section III. B.

FASD 4-Digit Code

Rank	**3** Growth	**4** Face	**3** Brain	**4** Prenatal Alcohol	3 Other Prenatal Risks	3 Other Postnatal Risks
4	severe	all 3 features	abnormal structure/neurology	high	high	high
3	moderate	2.5 features	severe dysfunction	some	some	some
2	mild	1-2 features	moderate dysfunction	unknown	unknown	unknown
1	normal	no features	normal function	none	none	none

FASD Umbrella

3 Diagnoses under the FASD Umbrella		Growth	FAS Face	Brain		Alcohol
1. FAS	Fetal Alcohol Syndrome	growth	face	severe		exposed
2. SE/AE	Static Encephalopathy / Alc-Exposed			severe		exposed
3. ND/AE	Neurodevelopmental Disorder / Alc-Exposed				moderate	exposed

Example above: If an individual presented with moderate growth deficiency, all 3 FAS facial features, severe brain dysfunction and high prenatal alcohol exposure, they would receive a 4-Digit Code 3434. Code 3434 is one of 40 codes that meet criteria for FAS (see Section V). FAS is one of three diagnoses under the umbrella of FASD. Other prenatal and postnatal risks are also ranked.

How are the 4 Digits Ranked?

The magnitude of expression of each feature is ranked independently on a 4-point Likert scale with 1 reflecting complete absence of the FASD feature and 4 reflecting a strong "classic" presence of the

FASD feature. The other prenatal and postnatal risks are also ranked on 4-point Likert scales. Specific criteria for each Rank are presented in Section III.B.

How Many 4-Digit Codes and Clinical Diagnostic Categories are There?

There are 256 possible 4-Digit Diagnostic Codes ranging from 1111 to 4444. The 256 codes and their corresponding clinical names are listed in numerical order in Section VI. Each 4-Digit Diagnostic Code falls into one of 19 unique Clinical Diagnostic Categories (labeled A through S) (see Sections IV and V). Only 108 of the 256 codes fall broadly under the umbrella of FASD in accordance with the FASD 4-Digit Code. These 108 codes are collapsed into 6 FASD diagnostic categories as portrayed in red font in Sections IV and V. These 6 FASD diagnostic categories are further collapsed into three clinically meaningful diagnostic categories under the umbrella of FASD: FAS, Static Encephalopathy/Alcohol-Exposed, and Neurodevelopmental Disorder/Alcohol-Exposed.

How Many of the Diagnostic Categories Fall Under the Umbrella of FASD?

Only 6 of the 19 diagnostic categories (A-E and J) fall broadly under the umbrella of FASD. These are highlighted in red font in Sections IV, V and VI). For example, 25% of the 4-Digit Codes end in 1 (Alcohol Rank 1, confirmed absence of prenatal alcohol exposure). An individual with confirmed absence of prenatal alcohol exposure cannot have FASD. Why keep 4-Digit Codes ending in 1 in this Diagnostic Guide? Codes ending in 1 help portray that the growth deficiency and brain abnormalities observed among individuals with prenatal alcohol exposure are also observed in individuals with confirmed absence of prenatal alcohol exposure. Presenting all combinations of 4-Digit Codes in this FASD diagnostic system also presents a valuable numeric method for classifying control or comparison groups in research studies designed to compare individuals with FASD to individuals with confirmed absence of prenatal alcohol exposure with and without adverse outcomes.

How are the Names of the Clinical Diagnostic Categories Constructed?

The following terms are used in varying combinations to name the 19 Diagnostic Categories. They include:

- **Sentinel Physical findings:**
  The term "S*entinel Physical Findings*" is used in this diagnostic system when the patient presents with growth deficiency at the Rank 3 or 4 level and/or presents with the FAS facial phenotype at the Rank 3 or 4 level. The term *"sentinel"* refers to the physical findings that are diagnostic indicators of FASD. These include a unique cluster of minor facial anomalies (short palpebral fissures, thin upper lip, and a smooth philtrum) and growth deficiency. Other physical findings (major or minor anomalies) may be detected instead of or in addition to these sentinel findings that may suggest alternate or additional conditions. There are places on the Diagnostic Form to record and interpret other physical findings.

- **Neurodevelopmental Disorder:**
  The term *"Neurodevelopmental Disorder"* is used to label the Diagnostic Category when the patient presents with functional impairments (cognitive, motor, language, etc) at the Brain Rank 2 level and no evidence of structural, neurological or functional abnormalities at the Brain Rank 3 or Rank 4 levels.

- **Static Encephalopathy:**
  The term *"encephalopathy"* refers to "any significant abnormal condition of the structure or function of brain tissues" (Anderson, 2002). The term *"static"* means that the abnormality in the brain is unchanging; neither progressing nor regressing. The term *"Static Encephalopathy"* is used in this diagnostic system when the patient presents with significant structural, neurological, and/or functional abnormalities that strongly support the presence of underlying brain damage at the Rank 3 and/or Rank 4 levels. The term does not define or suggest any specific pattern of structural, neurological, or functional abnormality.

Fetal Alcohol Syndrome

The term FAS is used to refer to patients who present with one of 40 4-Digit Diagnostic Code combinations reflecting growth deficiency; the FAS facial phenotype; significant structural, neurological, and/or functional brain abnormalities; and prenatal alcohol exposure confirmed by verbal or written record or the presence of the Rank 4 FAS facial phenotype (Astley & Clarren, 2001; (Astley) Hemingway, 2020). These 40 Codes are presented in Section V.

- **Alcohol (Exposed, Not Exposed, Exposure Unknown):**
  The last digit of the 4-Digit Code reflects prenatal alcohol exposure as determined through written or verbal documentation. The terms (Exposed) and (Not Exposed) are used when written or verbal documentation exists that confirms the presence or absence of exposure. If the presence or absence of exposure cannot be confirmed through written or verbal documentation, the term (Exposure Unknown) is applied. If exposure is ranked unknown, the Rank 4 FAS facial phenotype can serve as a proxy for confirmation of prenatal alcohol exposure. Alcohol exposure is reported independently of outcome(s) and does not imply that a causal association exists between the exposure and the outcome(s).

The names assigned to the 19 Diagnostic Categories (A-S) are listed in Sections IV and V. These names are constructed from the terms above and reflect the patient's clinical outcome and prenatal alcohol exposure. Five of the Diagnostic Categories A-E fall broadly under the umbrella of FASD as do 4 additional 4-Digit Codes in Category J that present with the Rank 4 FAS facial phenotype. Diagnostic Categories F and G reflect patients with confirmed prenatal alcohol exposure, who only present with growth and/or facial anomalies or no adverse outcomes whatsoever (normal growth, facial and brain outcomes). The 4-Digit Code does not consider these two diagnostic outcomes to be under the umbrella of FASD. The remaining 12 categories (H through S) reflect patients with unknown prenatal alcohol exposure or confirmed absence of prenatal alcohol exposure. These 12 categories present with the full spectrum of physical and functional abnormalities from normal to severe, but with a confirmed absence of prenatal alcohol exposure or the Rank 4 FAS facial phenotype do not fall under the umbrella of FASD.

Ultimately, establishing terms that are both clinically accurate, broadly applicable, and facilitate access to services remains a challenge. One of the greatest strengths of the 4-Digit Code is the assignment of a numeric 4-Digit Code to each patient that clearly captures the full spectrum of outcomes and exposure in the universal language of numbers. The 4-Digit Codes are independent of any proposed system for how to cluster them into diagnostic categories and what names to apply to each category.

How are the Names of the Clinical Diagnostic Categories Constructed?

- **Growth** deficiency and facial features are physical features. When either feature receives a Rank 3 or 4, *Sentinel physical finding(s)* is placed at the beginning of the name.
- When brain receives a Rank 3 or 4, the term *Static Encephalopathy* is included in the name. When **brain** receives only a Rank 2, the term *Neurodevelopmental Disorder* is included in the name.
- When **alcohol** exposure receives a Rank 3 or 4, *alcohol exposed* is placed at the end of the name. When alcohol exposure receives a Rank 2, *alcohol exposure unknown* is placed at the end of the name. When alcohol exposure receives a Rank 1, no *alcohol exposure* is placed at the end of the name.
- When the criteria for FAS are met, the term FAS is used in place of the more generic terms. For example, the term *FAS* would be used for the 4-Digit Code 3443 rather than *Sentinel physical finding(s) / static encephalopathy / alcohol exposed.*

FASD 4-Digit Code

	3	2	4 (2)	3		
Rank 4	severe	all 3 features	abnormal structure/neurology	high	high	high
3	moderate	2.5 features	severe dysfunction	some	some	some
2	mild	1-2 features	moderate dysfunction	unknown	unknown	unknown
1	normal	no features	normal function	none	none	none
	Growth	**Face**	**Brain**	**Prenatal Alcohol**	**Other Prenatal Risks**	**Other Postnatal Risks**

KEY

Growth and/or Face	Brain	Alcohol
Sentinel physical finding(s)	Static encephalopathy	Alcohol exposed
	Neurodevelopmental disorder	Alcohol exposure unknown

In the example above, the 4-Digit Code 3243 would receive the clinical name ***Sentinel physical findings / static encephalopathy / alcohol exposed*.** Note brain received both Rank 4 (for microcephaly) and Rank 2 (for moderate dysfunction). The higher brain Rank is used to derive the 4-Digit Code (3243). If brain receives a Rank 4, it is advised that both brain codes be reported as follows 324(2)3 conveying both the structural and functional status of the patient's brain. In another example, a code of 1222 would receive the clinical name *Neurodevelopmental disorder / alcohol exposure unknown*.

How to Explain the Diagnosis to the Patient

Generic summaries of each of the 19 Clinical Diagnostic Categories are presented in Section VII. These summaries can be used as the first page of the patient's final Medical Summary Note. Subsequent pages in the Medical Summary should document the findings and recommendations specific to the patient. We recommend the growth, face, brain, and exposure data, used to generate the 4-Digit Code, be reported in the Medical Summary to provide essential information for subsequent medical professionals and facilitate records-based public health surveillance efforts.

When sharing the diagnosis with caregivers, we have found that the following graphic provides a simple, clear way to present the results. Families receive a copy of this graphic at the end of the diagnostic appointment along with a comprehensive medical summary (see Section VII). We introduce FASD and the 4-Digit Code to the families as follows:

FASD is characterized by growth deficiency, minor facial anomalies, brain structural and/or functional impairment and prenatal alcohol exposure.

Each component is ranked on a 4-point scale. The higher the rank, the more severe the outcome or exposure.

Together, these ranks produce 4-Digit Codes that range from 1111 to 4444. A code of 1111 reflects an individual with normal growth, none of the FAS facial features, normal brain function and confirmed absence of prenatal alcohol exposure. A code of 4444 reflects an individual with the most severe presentation of FAS (severe growth deficiency, all 3 facial features of FAS, structural and/or neurological brain abnormalities and a confirmed high prenatal alcohol exposure

The 4-Digit Codes are grouped into three clinical diagnoses under the umbrella of FASD that reflect the full spectrum of FASD from moderate to severe. In the example presented, the 4-Digit Code 3434 is one of 40 codes that meet criteria for FAS.

As another example, Code 1134 reflects a person with normal growth, none of the 3 facial features of FAS, severe brain dysfunction and a high prenatal alcohol exposure. The Code 1134 meets criteria for SE/AE.

Other prenatal and postnatal risks may also be present and impact growth and development. These are also ranked on 4-point scales.

FASD 4-Digit Code

	3	**4**	**3**	**4**	3	3
Rank 4	severe	all 3 features	abnormal structure/neurology	high	high	high
3	moderate	2.5 features	severe dysfunction	some	some	some
2	mild	1-2 features	moderate dysfunction	unknown	unknown	unknown
1	normal	no features	normal function	none	none	none
	Growth	**Face**	**Brain**	**Prenatal Alcohol**	**Other Prenatal Risks**	**Other Postnatal Risks**

FASD Umbrella

3 Diagnoses under the FASD Umbrella		Growth	FAS Face	Brain	Alcohol
1. FAS	Fetal Alcohol Syndrome	growth	face	severe	exposed
2. SE/AE	Static Encephalopathy / Alc-Exposed			severe	exposed
3. ND/AE	Neurodevelopmental Disorder / Alc-Exposed			moderate	exposed

III. Instructions for Deriving the 4-Digit Code

B.1. Ranking Growth

What Type of Growth Deficiency Are We Looking For?

Growth deficiency plays an essential role in the diagnosis of FASD (Astley et al., 2016). Growth deficiency among individuals with prenatal alcohol exposure is highly correlated with and predictive of brain dysfunction. Growth deficiency can serve as a valuable marker for identifying infants with prenatal alcohol exposure at high risk for brain dysfunction that will typically not manifest until later in childhood.

We are looking for growth deficiency characteristic of a teratogenic insult, not characteristic of postnatal environmental factors such as nutritional deprivation or chronic or acute illness. We want to answer the question *'What is the patient's growth potential after controlling for parental height and postnatal environmental influences?'* Growth deficiency of teratogenic origin is likely to present as a relatively consistent impairment over a period of time (i.e., the patient's growth follows the normal curve, but is below genetic expectation for family background). In contrast, growth deficiency due to postnatal environmental influences (e.g., illness, nutritional deprivation, etc.) is likely to present as periodic fluctuations in the curve.

The method described below allows one to rank a patient's overall growth pattern on a single 4-point Likert scale with 1 equal to 'normal' and 4 equal to "significantly deficient". Not all patients will have complete growth curves available, therefore, a guide is provided below for prioritizing the ranking of the patient's growth over a lifetime.

How to Measure and Rank Growth: The 1st Digit of the 4-Digit Diagnostic Code

A. The height percentile should be adjusted for age and sex. Because there is a significant genetic component in attained stature, adjustment for mid-parent stature is also recommended when both parents' heights are known. Himes et. al., (1985) provide charts for mid-parent adjustment of recumbent length (birth to 3 years) and stature (3 to 18 years) of US children relative to National Center for Health Statistics growth charts.

B. The weight percentile should be adjusted for age and sex. Weight is not adjusted for height.

   Clinicians are encouraged to use the most current electronic growth charts that best match the age, sex, race/ethnicity and country of origin of each patient.

C. For ranking purposes, the growth record is separated into two parts:
   1. Prenatal growth (birth measures)
   2. Postnatal growth (all measures collected after birth)

   Select the part of the growth record with the greatest deficiency in the height percentile.

   If the prenatal height percentile is lower than all postnatal height percentiles, proceed to section D for instructions on how to rank prenatal growth.

If any of the postnatal height percentiles are lower than the prenatal height percentile, select the point or consecutive points in the growth record that reflect the lowest height percentiles that cannot be attributed to postnatal environmental influences such as nutritional deprivation or chronic illness. If the height deficiency is reflected in a series of points in the growth record, as opposed to a single point, rank the level of deficiency based on the percentile range where the majority of the points fall. Proceed to section D for instructions.

D. Rank the level of deficiency of the height and weight percentiles, for the part of the growth record with greatest deficiency in the height percentile by circling A, B, or C in the ABC-Score table at the bottom of page 1 of the FASD Diagnostic Form. Tables 1 and 2 below are also printed on the electronic images of the Lip-Philtrum Guides. This ABC-Score table is duplicated below as Table 1. The height and weight percentiles selected for ranking should be matched sets. For example, if the height at 10 years of age is selected for ranking, the corresponding weight percentile at 10 years of age should also be selected for ranking. One does not rank the height at one age and the weight at another age to generate an ABC-Score.

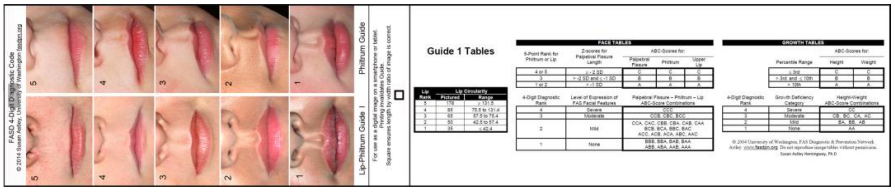


Table 1: Deriving the ABC-Score for Growth

	Circle the ABC-Scores for:	
Percentile Range	Height	Weight
≤ 3rd	C	C
>3rd and ≤ 10th	B	B
>10th	A	A

E. Next, refer to Table 2 to determine the *4-Digit Diagnostic Rank* of the Height-Weight ABC-Score recorded in Table 1. Transfer the resulting 4-Digit Diagnostic Rank for growth to the 4-Digit Diagnostic Code Grid at the top of page 1 of the FASD Diagnostic Form (Section II).

Table 2: Converting the Growth ABC-Score to a 4-Digit Diagnostic Rank for Growth

4-Digit Diagnostic Rank	Growth Deficiency Category	Height-Weight ABC-Score Combinations
4	Severe	CC
3	Moderate	CB, BC, CA, AC
2	Mild	BA, BB, AB
1	None	AA

Normal Growth Charts

Height, Weight, OFC:
Clinicians are encouraged to use the most current electronic charts for height, weight and head circumference that best match the age, sex, race/ethnicity, and country of origin of each patient. In our Seattle WA FASDPN clinic, we currently use the CDC, WHO and Rollins et al (2010) growth charts for OFC,, weight and height and adjust for mid-parental height (Himes et al., 1985) when both parents' heights are available.

Facial Measures:
We recommend using the free FAS Facial Photographic Analysis Software (Astley, 2016) distributed by the FASDPN to obtain the most accurate measures of the facial features (Astley, 2015). The Facial Software incorporates an adjustment factor that is confirmed to accurately measure a palpebral fissure length from a 2-dimensional digital photo within 0.2 mm of the gold standard of measure (a sliding digital caliper). We do not recommend using a handheld ruler to measure PFLs. Numerous studies have confirmed the inaccuracy of the ruler method (Astley, 2015). The FASDPN currently uses the Iosub African American PFL charts (Iosub et al., 85) for individuals that are full or half African American and the Stromland Scandinavian PFL charts for all other races (Stromland et al., 1999). These charts come with our FAS Facial software and are available in our free excel PFL Z-score calculator. The Hall Caucasian PFL charts (1989) are no longer in use (Clarren et al., 2010).

Example for Scoring Growth Deficiency

Patient's Growth Record:

	Age (years)	Height Percentile	Weight Percentile
birth	0.0	8 %	1 %
	1.5	14 %	16 %
	5.0	12 %	15 %
	7.0	12 %	15 %
	15.5	15 %	15 %

Assume in this case the clinical records rule-out any adverse environmental influence on the postnatal measures and mid-parental height is unknown.

Ranking:

- Priority would be placed on ranking the birth length and weight because the birth length percentile is lower than all postnatal height percentiles recorded.
- Birth length (8 %) would receive an **ABC-Score = B** (> 3rd and ≤ 10th percentile) (Table 1).
- Birth weight (1 %) would receive an **ABC-Score = C** (≤ 3rd percentile) (Table 1).
- The Height-Weight ABC-Score combination would be **BC** (Table 1).

Table 1: Deriving the ABC Score for Growth

	Circle the ABC-Scores for:	
Percentile Range	Height	Weight
≤ 3rd	C	**C**
>3rd and ≤ 10th	**B**	B
>10th	A	A

- The Height-Weight ABC-Score of **BC** reflects **Moderate** growth deficiency (Table 2)
- **Moderate** growth deficiency would receive a **Rank 3** in the 4-Digit Diagnostic Code (Table 2).

Table 2: Converting the Growth ABC-Score to a 4-Digit Diagnostic Rank for Growth

4-Digit Diagnostic Rank	Growth Deficiency Category	Height-Weight ABC-Score Combinations
4	Severe	CC
3	**Moderate**	CB, **BC**, CA, AC
2	Mild	BA, BB, AB
1	None	AA

- **Rank 3** would be transferred to the 4-Digit Diagnostic Code Grid on page 1 of the FASD Diagnostic Form (as duplicated below).

Result:

FASD 4-Digit Code

Rank	**3** Growth	Face	Brain	Prenatal Alcohol	Other Prenatal Risks	Other Postnatal Risks
4	severe	all 3 features	abnormal structure/neurology	high	high	high
3	moderate	2.5 features	severe dysfunction	some	some	some
2	mild	1-2 features	moderate dysfunction	unknown	unknown	unknown
1	normal	no features	normal function	none	none	none

III. Instructions for Deriving the 4-Digit Code

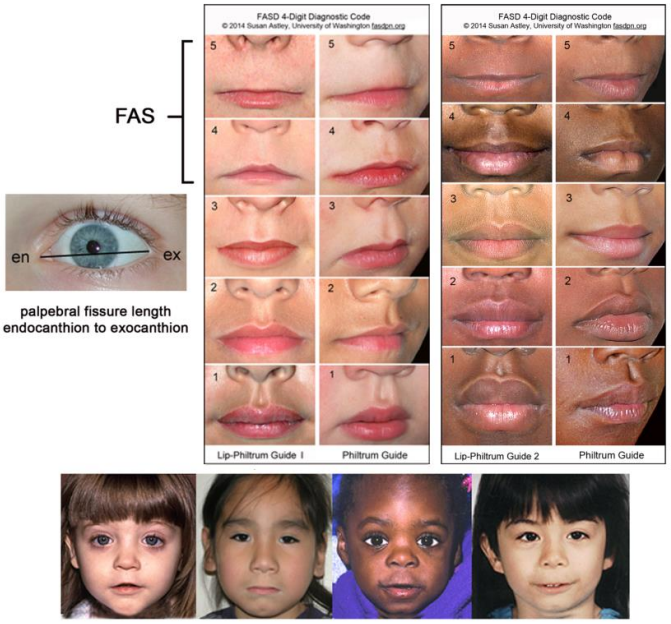
B.2. Ranking the Facial Phenotype

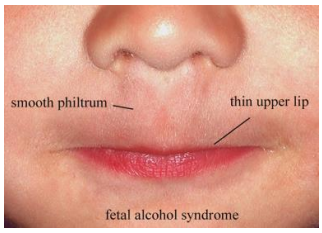
The FAS Facial Phenotype

The face of FAS is defined by the 4-Digit Code as the simultaneous expression of three facial features:

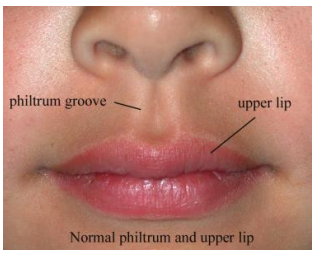
1. Short palpebral fissure lengths (2 or more standard deviations below the mean)
2. Smooth philtrum (Rank 4 or 5 on the University of Washington Lip-Philtrum Guides).
3. Thin upper lip (Rank 4 or 5 on the University of Washington Lip-Philtrum Guides).

If facial measures are available at different ages, the age when the expression of the FAS facial phenotype is most severe (highest Face Rank) should be used.





Rank 5 lip and philtrum



Rank 1 lip and philtrum

Three facial features of FAS. Examples of the University of Washington 4-Digit Code Rank 4 FAS facial phenotype (small eyes, smooth philtrum, and thin upper lip) across four races: Caucasian, Native American, African American, Asian American. © Susan Hemingway PhD

David Smith, M.D., who coined the term FAS in 1973, identified these features as the *key* diagnostic facial features in 1979 (Smith, 1979). A series of empirical studies conducted over the next 30 years confirmed: 1) The 4-Digit-Code Rank 4 FAS facial phenotype is the only facial phenotype that provides sufficient positive predictive value (PPV) and specificity (100%) to prenatal alcohol exposure (PAE) to allow the facial phenotype to serve as confirmation of alcohol exposure in a diagnostic setting when PAE is unknown. Even minimal relaxation of the phenotype (e.g., Face Rank 3) results in PPV (35%) and specificity (88.7%) values too low to use as confirmation of PAE. (Astley

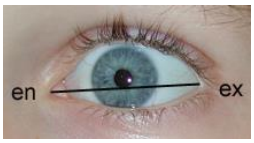
& Clarren, 1996, 2000, 2001; Astley-Hemingway et al., 2020). The clinical validity of these features has been confirmed through population-based screening and surveillance studies (Astley et al., 2002; Astley, 2004a) and empirical studies documenting remarkably strong correlations between these midline facial anomalies and decreased volume of the frontal lobe (Astley et al., 2009). The FAS facial phenotype presents on a clinically meaningful continuum. As the FAS facial phenotype increases in severity of expression from Rank 1 to Rank 4, the prevalence and severity brain damage/dysfunction, growth deficiency and prenatal alcohol exposure increase significantly (Astley et al., 2013).

How to Measure and Rank the Face: The 2nd Digit of the 4-Digit Diagnostic Code

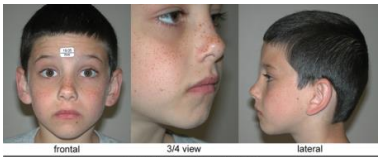
There are two methods for measuring the 3 facial features of FAS: 1) direct measurement and 2) computerized analysis of a 2-dimensional digital facial photograph using the FAS Facial Photographic Analysis Software developed by the University of Washington FASDPN. The latter is confirmed more accurate (Astley & Clarren, 2001; Astley, 2015). A video demonstration of the software is available online. The FAS Facial Photographic Analysis Software 2016 v2.1 is available free from the FASDPN website. Animations demonstrating proper measurement technique are also available.

A. Palpebral Fissure Length (PFL)

Direct Measurement: The PFL is the distance from the endocanthion (en) to the exocanthion (ex). The PFLs can be measured to the nearest mm with a clear plastic, 15-cm ruler, held as close as possible to the eye without touching the eye or eyelashes. The patient is asked to open their eyes fully to allow accurate identification of the endocanthion and exocanthion landmarks (Astley & Clarren, 1996; Farkas, 1994). Numerous published studies have confirmed the inaccuracy of measuring PFLs with a ruler (Astley, 2015). Although sliding digital calipers are the most accurate method of measurement, use of calipers is too dangerous. The FASDPN recommends all facial features, including the PFLs be measured using the free FAS Facial Photographic Analysis Software 2016 v2.1.



Digital Photographic Measurement: Three standardized 2-dimensional digital photos of the face are taken with a ¾ inch machine-cut paper sticker placed between the eyebrows to serve as an internal measure of scale (e.g., a ruler in the photo) (Astley, 2015). Write the size of the sticker on the sticker. The camera is held 4 feet from the face to avoid lens distortion.



Standardized Photo Set

The digital images are analyzed using the FAS Facial Photographic Analysis Software (Astley, 2016). View a video demonstration of the software. The PFL is measured by clicking the mouse curser on the endocanthion and exocanthion landmarks of the right and left eyes. The length of each palpebral fissure and its z-score (number of standard deviations above or below the norm) are computed automatically based on formulas and normal charts embedded in the software. More detailed instructions are provided with the software.

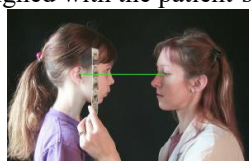
Ranking the PFL*:* The PFL is ranked according to its z-score (or how many standard deviations above or below the mean it is on a normal PFL growth chart) using the Face Tables on the backside of the Lip-Philtrum Guides (Figure 2). If the eyes are substantially different in size, (more than 2

mm different) rank the larger PFL. If the eyes are comparable in size, rank the mean of the right and left PFL. The FASDPN currently uses the Iosub African American PFL charts (Iosub, 1985) for individuals that are full or half African American and the Stromland Scandinavian PFL charts for all other races (Stromland, 1999). These charts come with the FAS Facial software and are available in our free Excel PFL Z-score calculator posted online. The Hall Caucasian PFL charts for birth to 16 years (1989) are no longer used and should not be used (Clarren et al., 2010).

B. Upper Lip Thinness and Philtrum Smoothness

Direct Measurement: Upper lip thinness (the red or vermilion portion of the upper lip) and philtrum smoothness are measured independent of one another using the 5-point pictorial Likert scale presented on the University of Washington Lip-Philtrum Guides (see Figure 2 below). Guide 1 is used for Caucasians and any race or racial mix with lips similar in thickness to Caucasians. Guide 2 is used for African Americans and any race or racial mix with lips similar in thickness to African Americans (e.g., aboriginal Australians). Which Guide was selected should be reported in the medical summary. The physician holds the Lip-Philtrum Guide next to the patient's face and identifies the picture that best matches the patient's upper lip and identifies the picture that best matches the patient's philtrum.

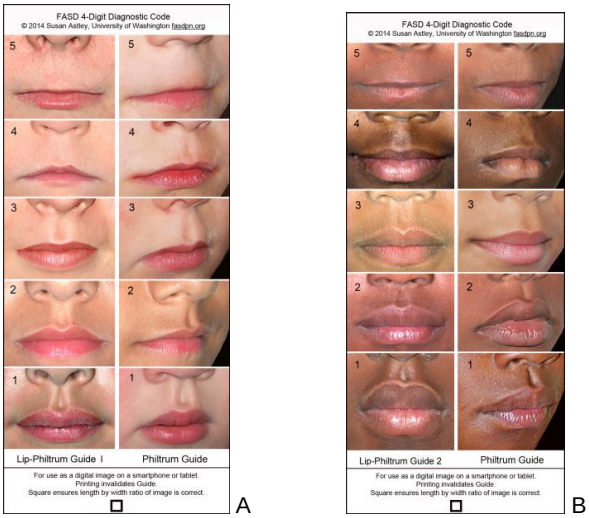
When measuring the upper lip thinness, the physician's eyes need to be aligned with the patient's Frankfort horizontal plane. The Frankfort horizontal plane is defined by a line (green line) that passes through the patient's external auditory canal and the lowest border of the bony orbital rim (orbitale). The physician's eyes (or camera lens) should be directly in line with this plane. If the physician stood above this plane looking down on the patient, the patient's upper lip could appear thinner than it truly is. View this animation demonstrating how to align yourself in the patient's Frankfort horizontal plane.

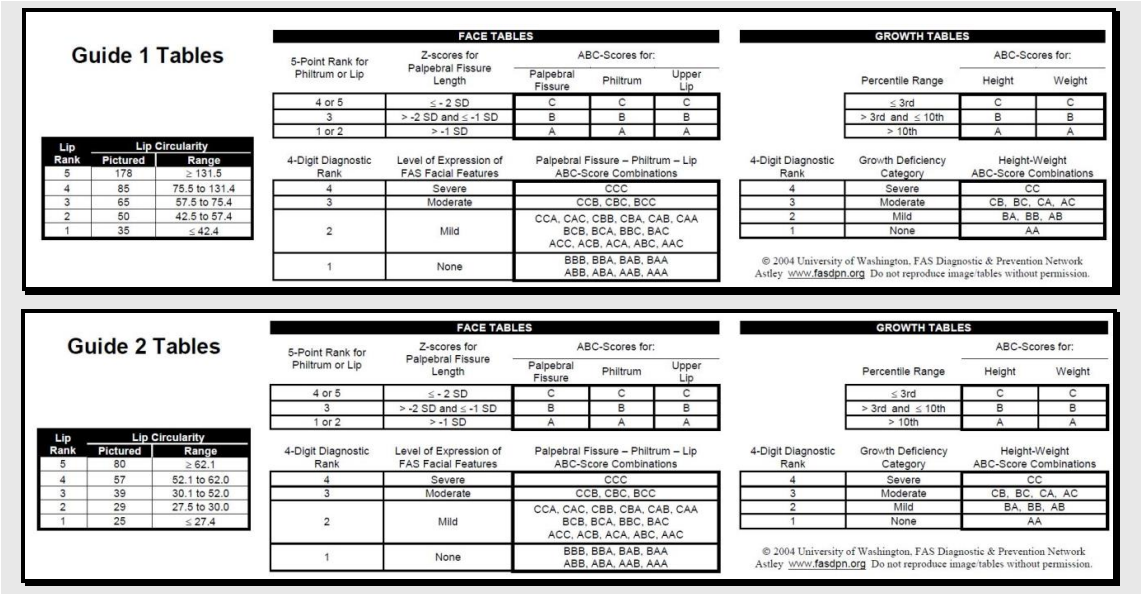


Lips must be *gently closed with no smile* to accurately measure philtrum smoothness and upper lip thinness (Astley et al., 1999). This is the same child with and without a smile. A smile makes the philtrum appear smoother and the upper lip thinner than they truly are. Note that without a smile, the lip and philtrum would both receive a correct Rank 2 on the Caucasian Lip-Philtrum Guide 1. With a smile, the lip and philtrum would both receive an *incorrect* Rank 5.

Digital Photographic Measurement: Lip thinness is measured from the frontal photograph using the FAS Facial Photographic Analysis Software. The red (e.g. vermilion) portion of the upper lip in the frontal photograph is outlined with the mouse to compute circularity (perimeter^2/area). The thinner the upper lip, the bigger the circularity.

Pictured is an example of the upper lip outlined to compute circularity. The circularity of this lip is 44.2, which is equivalent to Rank 2 on Lip-Philtrum Guide 1. Each Rank on the Lip-Philtrum Guide is defined by a range of circularities (See the Face Tables printed with the Lip-Philtrum Guide 1 in Figure 2 below). The software automatically ranks lip thinness using the circularity measure. The philtrum is measured by selecting the ¾ view picture on the University of Washington Lip-Philtrum Guide that best matches the patient's philtrum. More detailed instructions are provided in the software Instruction Manual.





Guide 1 Tables

Lip Rank	Lip Circularity Pictured	Lip Circularity Range
5	178	≥ 131.5
4	85	75.5 to 131.4
3	65	57.5 to 75.4
2	50	42.5 to 57.4
1	35	≤ 42.4

FACE TABLES

5-Point Rank for Philtrum or Lip	Z-scores for Palpebral Fissure Length	ABC-Scores for: Palpebral Fissure	Philtrum	Upper Lip
4 or 5	≤ - 2 SD	C	C	C
3	> -2 SD and ≤ -1 SD	B	B	B
1 or 2	> -1 SD	A	A	A

4-Digit Diagnostic Rank	Level of Expression of FAS Facial Features	Palpebral Fissure – Philtrum – Lip ABC-Score Combinations
4	Severe	CCC
3	Moderate	CCB, CBC, BCC
2	Mild	CCA, CAC, CBB, CBA, CAB, CAA BCB, BCA, BBC, BAC ACC, ACB, ACA, ABC, AAC
1	None	BBB, BBA, BAB, BAA ABB, ABA, AAB, AAA

GROWTH TABLES

Percentile Range	ABC-Scores for: Height	Weight
≤ 3rd	C	C
> 3rd and ≤ 10th	B	B
> 10th	A	A

4-Digit Diagnostic Rank	Growth Deficiency Category	Height-Weight ABC-Score Combinations
4	Severe	CC
3	Moderate	CB, BC, CA, AC
2	Mild	BA, BB, AB
1	None	AA

Guide 2 Tables

Lip Rank	Lip Circularity Pictured	Lip Circularity Range
5	80	≥ 62.1
4	57	52.1 to 62.0
3	39	30.1 to 52.0
2	29	27.5 to 30.0
1	25	≤ 27.4

FACE TABLES

5-Point Rank for Philtrum or Lip	Z-scores for Palpebral Fissure Length	ABC-Scores for: Palpebral Fissure	Philtrum	Upper Lip
4 or 5	≤ - 2 SD	C	C	C
3	> -2 SD and ≤ -1 SD	B	B	B
1 or 2	> -1 SD	A	A	A

4-Digit Diagnostic Rank	Level of Expression of FAS Facial Features	Palpebral Fissure – Philtrum – Lip ABC-Score Combinations
4	Severe	CCC
3	Moderate	CCB, CBC, BCC
2	Mild	CCA, CAC, CBB, CBA, CAB, CAA BCB, BCA, BBC, BAC ACC, ACB, ACA, ABC, AAC
1	None	BBB, BBA, BAB, BAA ABB, ABA, AAB, AAA

GROWTH TABLES

Percentile Range	ABC-Scores for: Height	Weight
≤ 3rd	C	C
> 3rd and ≤ 10th	B	B
> 10th	A	A

4-Digit Diagnostic Rank	Growth Deficiency Category	Height-Weight ABC-Score Combinations
4	Severe	CC
3	Moderate	CB, BC, CA, AC
2	Mild	BA, BB, AB
1	None	AA

Figure 2. University of Washington Lip-Philtrum Guides 1 (A) and 2 (B) are used to rank upper lip thinness and philtrum smoothness. The philtrum is the vertical groove between the nose and upper lip. The guides reflect the full range of lip thickness and philtrum depth with Rank 3 representing the population mean. Ranks 4 and 5 reflect the thin lip and smooth philtrum that characterize the FAS facial phenotype. Guide 1 is used for Caucasians and any race or racial mix with lips indigenously similar in thickness to Caucasians. Guide 2 is used for African Americans and any race or racial mix with lips indigenously similar in thickness to African Americans. Free digital images of these Guides and Tables for loading on a cell phone are available from astley@uw.edu. Circularity is perimeter^2/area and is measured using the FAS Facial Photographic Analysis Software (Astley, 2016). © Susan (Astley) Hemingway PhD.

C. Deriving the Facial ABC-Score

Rank the mean palpebral fissure length, philtrum smoothness, and upper lip thinness by circling A, B, or C in each column in the ABC-Score printed on the backside of the Lip-Philtrum Guide (Figure 2). This table is duplicated below as Table 1. The three facial features must be measured at the same age. In other words, one would NOT rank the philtrum at 10 years of age and the PFL and lip at 15 years of age. If facial measures are available at more than one age, rank the age when the expression of the FAS facial phenotype is most severe (has the highest Face Rank).

Table 1: Deriving the ABC-Score for Facial Phenotype

5-Point Likert Rank for Philtrum & Lip	Z-score* for Palpebral Fissure Length	Circle the ABC-Scores for: Palpebral Fissure	Philtrum	Upper Lip
4 or 5	≤ -2 SD	C	C	C
3	>-2 SD and ≤ -1 SD	B	B	B
1 or 2	> -1 SD	A	A	A

* Z-Score = (patient's mean PFL - mean PFL for a normal population) / (standard deviation of the mean PFL for a normal population)

Use the FAS Facial Photographic Analysis Software or the PFL Z-score Calculator to compute the z-score.

The z-score reflects how many standard deviations above or below the mean the patient's PFL is.

D. Deriving the 4-Digit Rank for Face: The 2nd Digit in the 4-Digit Code

Next, refer to Table 2 to determine the *4-Digit Diagnostic Rank* based on the ABC-Score derived from Table 1. Transfer the resulting 4-Digit Diagnostic Rank for face to the 4-Digit Diagnostic Code Grid on page 1 of the FASD Diagnostic Form (Section 11).

Table 2: Converting the Facial ABC-Score to a 4-Digit Diagnostic Rank for Face

4-Digit Diagnostic Rank	Level of Expression of FAS Facial Features	Palpebral Fissure - Philtrum - Lip ABC-Score Combinations
4	Severe	CCC
3	Moderate	CCB, CBC, BCC
2	Mild	CCA, CAC, CBB, CBA, CAB, CAA BCB, BCA, BBC, BAC ACC, ACB, ACA, ABC, AAC
1	None	BBB, BBA, BAB, BAA ABB, ABA, AAB, AAA

Example: Ranking the Facial Phenotype

Patient Facial Measures at 10 Years of Age (male, Caucasian):

- **Mean PFL = 24.5 mm**: Left PFL = 24.6 mm. Right PFL = 24.4 mm.

  Mean PFL Z-score = -2.16 using Stromland's PFL growth charts for Caucasian males (Stromland, 1999).

  - Note: a normal PFL for a 10-year-old male using Stromland's PFL chart =27.43 mm.
  - Use the FAS Facial Photographic Analysis Software or the PFL Z-score Calculator to compute the Z-score.

- Philtrum smoothness received a **Rank 5** on the Caucasian Lip-Philtrum Guide (Figure 2).

- The circularity of the upper lip was 65.5. Thus, upper lip thinness received a **Rank 3** on the Caucasian Lip-Philtrum Guide (Figure 2 above). The circularity range for Rank 3 is 57.5 to 74.9.

Ranking

- The mean PFL z-score of -2.16 receives an **ABC-Score = C** (≤ -2 SD) (Table 3).
- The Rank 5 philtrum receives an **ABC-Score = C** (Table 3).
- The Rank 3 upper lip receives an **ABC-Score = B** (Table 3).
- The ABC-Score combination for Palpebral Fissure - Philtrum - Lip is **CCB** (Table 3).

Table 3: Deriving the ABC-Score for Facial Phenotype

5-Point Likert Rank for Philtrum & Lip	Z-score for Palpebral Fissure Length	Circle the ABC-Scores for: Palpebral Fissure	Philtrum	Upper Lip
4 or 5	≤ -2 SD	**C**	**C**	C
3	>-2 SD and ≤ -1 SD	B	B	**B**
1 or 2	> -1 SD	A	A	A

- The Facial ABC-Score of **CCB** reflects a **Moderate** level of expression of the FAS facial phenotype (Table 4).
- A **Moderate** expression of the FAS facial phenotype would receive a **Rank 3** in the 4-Digit Diagnostic (Table 4).

Table 4: Converting the Facial ABC-Score to a 4-Digit Diagnostic Rank

4-Digit Diagnostic Rank	Level of Expression of FAS Facial Features	Palpebral Fissure - Philtrum - Lip ABC-Score Combinations
4	Severe	CCC
3	**Moderate**	**CCB**, CBC, BCC
2	Mild	CCA, CAC, CBB, CBA, CAB, CAA, BCB, BCA, BBC, BAC ACC, ACB, ACA, ABC, AAC
1	None	BBB, BBA, BAB, BAA ABB, ABA, AAB, AAA

- **Rank 3** would be transferred to the 4-Digit Diagnostic Code Grid on page 1 of the FASD Diagnostic Form (as duplicated below).

Result:

FASD 4-Digit Code

3

Rank	Growth	Face	Brain	Prenatal Alcohol	Other Prenatal Risks	Other Postnatal Risks
4	severe	all 3 features	abnormal structure/neurology	high	high	high
3	moderate	2.5 features	severe dysfunction	some	some	some
2	mild	1-2 features	moderate dysfunction	unknown	unknown	unknown
1	normal	no features	normal function	none	none	none

The FAS Facial Photographic Analysis Software produces a 1-page summary report for entry into the patient's medical record. Below is an example of an individual with none of the FAS facial features.

FAS Facial Photographic Analysis Report

IDENTIFICATION

Name	John (First)	T (Middle)	Doe (Last)
Subject I.D.	None		
Source of Photo	Clinic		
Gender	Male		
Race	Caucasian/Caucasian		
Birth Date	1/1/1990		

PHOTO ASSESSMENT

Normal PFL Chart: Scandinavian (Stromland '99) Lip-Philtrum Guide: Caucasian
Normal ICD Chart: Caucasian (Hall '89)

	Frontal	¾ View	Lateral
File Name	Demo Frontal	Demo 3/4	Demo Lateral
Date of Photo	6/22/1998	6/22/1998	6/22/1998
Age (yrs) in photo	8.47	8.47	8.47
Date of Photo Assessment	6/22/1998	6/22/1998	6/22/1998
Photo Assessor	Astley	Astley	Astley

Length of Real Internal Measure of Scale(sticker) placed on forehead (mm): 19.05
Length of Internal Measure of Scale in Frontal Photo (pixels): 155.2

Left Palpebral Fissure Length:	In photo (pixels) 208.5	True Length (mm) 28.2	Z-score 1.04
Right Palpebral Fissure Length:	In photo (pixels) 205.5	True Length (mm) 27.7	Z-score 0.67
Mean Palpebral Fissure Length:	In photo (pixels) 207.0	True Length (mm) 28.0	Z-score 0.86
Inner Canthal Distance (ICD):	In photo (pixels) 200.0	True Distance (mm) 24.5	Z-score -2.22

Flat Philtrum (5-point rank): In Frontal Photo 3 In ¾ Photo 3

Thin Upper Lip: Circularity (perimeter²/area) 44.2 5-Point rank (Circ) 2 5-Point rank (Scale) 2

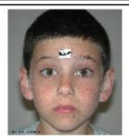
clown eyebrows ☐ ptosis ☐ strabismus ☐ epicanthal folds ■
flat midface ☐ protruding ears ☐ flat nasal bridge ☐ hypertelorism ☐

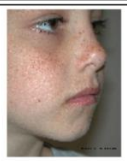
Other anomalies present: hypotelorism

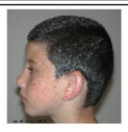
Comments:
Other syndromes present: None reported

PHOTO QUALITY

	Frontal	¾ View	Lateral
Side showing		Right	Left
Head rotation (5-point rank/degrees) to subject's Right (+) or Left (-)	0°	0	0
Head tilt (5-point rank) toward subject's Right (+) or Left (-) shoulder			0
Head tip (degrees) Up (+) or Down (-) from Frankfort Horizontal Plane	0°		
Exposure (3-point rank)	1 (good)	1 (good)	1 (good)
Focus (3-point rank)	1 (good)	1 (good)	1 (good)
Facial Expression (3-point rank)	1 (Relaxed)	1 (Relaxed)	1 (Relaxed)
Reliability of ABC-Score for palpebral fissure length (5-point rank)	1 (very good)		
Reliability of ABC-Score for philtrum (5-point rank)	1 (very good)	1 (very good)	
Reliability of ABC-Score for upper lip (5-point rank)	1 (very good)		


Demo Frontal


Demo 3/4


Demo Lateral

OUTCOME

	A (PFL)	B (Philtrum)	A (Lip)
ABC-Score	A	B	A
Data Used	mean	3/4 view	circularity

4-Digit Diagnostic Code for Face: 1: FAS features absent

III. Instructions for Deriving the 4-Digit Code
B.3. Ranking the Brain

Alcohol's Impact on the Developing Brain

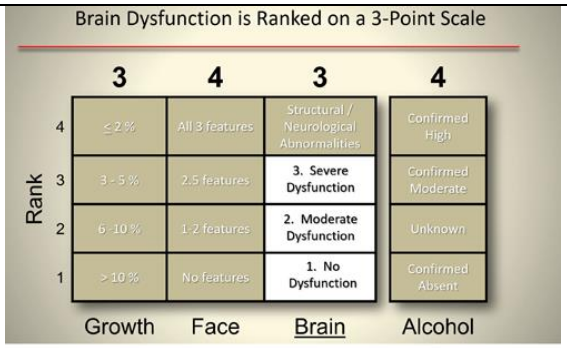
Alcohol is a teratogen that can alter the developing brain in a variety of ways from gross structural anomalies to subtle alterations in neurochemical levels (Stratton et al., 1996; West, 1986). Alterations in brain structure and/or chemistry can lead to altered brain function. Our ability to detect structural, neurological, and functional brain abnormalities is dependent on the sensitivity of today's measurement tools, which will continue to improve over time. Not all structural or neurological abnormalities result in *measurable* dysfunction and not all functional abnormalities are due to underlying brain damage. Some functional abnormalities result from adverse postnatal environmental factors and are transient in nature if the environment is improved.

How to Rank Brain: The 3rd Digit of the 4-Digit Diagnostic Code

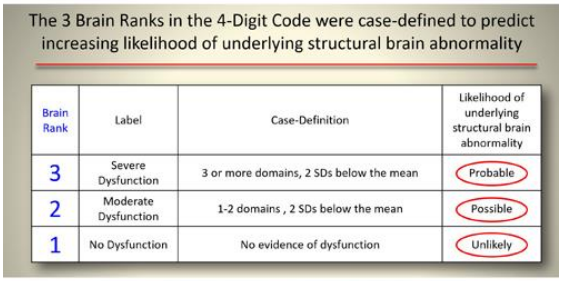
The 4-point Likert Scale for Brain documents: 1) that individuals with prenatal alcohol exposure can present with structural, neurological and/or functional brain abnormalities and 2) that these brain abnormalities occur along a continuum of severity.

An important point to keep in mind is that the Brain scale performs as two scales in one. In its first use, the full scale (from 1 to 4) documents increasing "probability" of underlying brain damage based on structural, neurological, and/or functional evidence. *The higher the Rank from 1 to 4, the stronger the evidence or higher the probability that there is underlying brain damage (Figure 3)* (Astley, 2013, Astley et al., 2009). In its second use, the scale (from 1 to 3) also documents increasing severity of brain dysfunction. *The higher the Rank from 1 to 3, the more severe and global the dysfunction.*

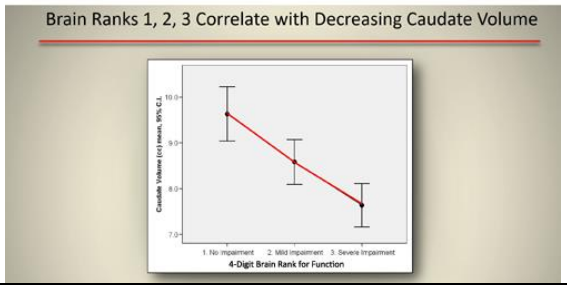
The descriptive labels assigned to Ranks 1 through 4 reflect the increasing probability that underlying brain damage exists. Rank 4 is labeled "definite" because structural/neurological abnormalities are definitive evidence of brain damage. Ranks 1, 2, and 3 are labeled "unlikely", "possible", and "probable" evidence of brain damage, respectively, because measures of dysfunction are not definitive evidence of underlying brain damage, but the probability of underlying brain damage increases with increasing severity of dysfunction. Data from the University of Washington FASDPN show this to be true. Among the first 1,500 patients diagnosed, those presenting with Rank 2 or Rank 3 level dysfunction had a 5.8-fold and 10.8-fold increased risk of having structural/neurological brain damage, respectively, relative to patients with no evidence of dysfunction (Rank 1). This correlation between brain function and structure was also confirmed in our FASD MRI study. The more severe the Brain Rank for function, the smaller the volume of the frontal lobe (Fig 12 from (Astley, 2013; Astley et al., 2009) below. As stated in the Institute of Medicine report (Stratton et al., 1996) "FAS can be characterized by behavioral or cognitive problems that are thought to result from *organic brain damage*, are not easily related to genetic background or environmental influences and may be resistant to improvement with traditionally effective intervention techniques".



A



B



C

Figure 12 from (Astley, 2013). A) The 4-Digit Code ranks brain dysfunction on a 3-point scale (none, moderate, severe). B) The 3 Brain Ranks were case-defined to predict increasing likelihood of underlying structural brain abnormality. C) MRI confirmed this to be true (Astley et al., 2009). The more severe the brain dysfunction (Rank 1, 2, 3), the smaller the caudate volume (significant linear trend F=13.5; p<.001; Duncan range test confirms each brain group is significantly distinct from the others).

All patients receive a Rank 1, 2 or 3 to document their level of brain dysfunction. Patients who present with significant structural and/or neurological evidence of brain damage will also receive a Rank 4. Thus, all patients with structural/neurological evidence of brain damage will have two Brain Ranks, one documenting their structural/neurological damage (Rank 4) and one documenting their level of dysfunction (Rank 1, 2 or 3). More specifically, they will receive either: (a) Brain Ranks 4 and 3 (structural/neurological damage with Rank 3 level dysfunction); (b) Brain Ranks 4 and 2 (structural/neurological damage with Rank 2 level dysfunction); or (c) Brain Ranks 4 and 1 (structural/neurological damage with no current evidence of dysfunction). When two Brain Ranks are applicable, the 4-Digit Code and Diagnostic Category are based on the *highest* Brain rank received, for it reflects the highest level of certainty there is underlying Brain damage. Both Brain

ranks should be circled in the Brain Column of the Diagnostic Grid and both numbers would be inserted in the Diagnostic Code with the lower Rank placed in parentheses 4(3). (See 4-Digit Diagnostic Code grid below). The Diagnostic Category would be based on the highest Rank in the Brain column.

FASD 4-Digit Code

4 (3)

Rank	Growth	Face	Brain	Prenatal Alcohol	Other Prenatal Risks	Other Postnatal Risks
4	severe	all 3 features	abnormal structure/neurology	high	high	high
3	moderate	2.5 features	severe dysfunction	some	some	some
2	mild	1-2 features	moderate dysfunction	unknown	unknown	unknown
1	normal	no features	normal function	none	none	none

Definitions of Brain Ranks 1 through 4.

Brain Rank 4: (Structural/Neurological Abnormalities) "Static Encephalopathy" "Definite" Evidence of Brain Damage.

Rank 4 Description: This rank is selected when the evidence for brain damage is defined through a traditional medical approach. It is our impression that "brain damage" or "static encephalopathy" is readily diagnosed by physicians when 'significant' structural abnormalities of the brain are detected or when neurological findings of presumed prenatal origin are found.

Structural evidence of brain damage may include, but is not limited to:

1. Microcephaly, defined as an occipital frontal circumference (OFC) 2 or more standard deviations below the mean. Head circumference 2 or more standard deviations below the mean has long been associated with functional impairment in the literature (Dolk, 1991; Pryor & Thelander, 1968). Among 999 patients with prenatal alcohol exposure evaluated at the FASDPN, those with microcephaly have IQs that on average are 10 points lower than those with normal head circumferences.

2. Significant brain abnormalities of presumed prenatal origin observable through imaging techniques. Abnormalities may include, but are not limited to hydrocephaly, heterotopias, and change in shape and/or size of brain regions. These abnormalities should be determined by appropriately trained medical professionals.

Neurological evidence of brain damage may include, but is not limited:

1. Seizures not due to a postnatal insult or other postnatal events.

2. Other hard neurological signs of presumed prenatal origin (e.g. cerebral palsy, tick disorders).
3. Hearing loss. Among children evaluated at the FASDPN, neurosensory hearing loss was 16-fold more prevalent among children with FAS (40%) than among children with other FASDs (2.4%) (McLaughlin et al., 2019), for whom the prevalence of hearing loss was similar to that estimated for the general U.S. adolescent population (2.3%) (Lin, et al., 2011)

***Rank 4 Criteria*:** At least one "significant" structural or neurological finding is required for a classification of Brain Rank 4 (Table 5). A significant finding is one that is 2 or more standard deviations below the mean if measured on a standardized scale or deemed "clinically significant" when assessed by an appropriate trained professional like a clinical radiologist or neurologist.

Documenting the Evidence that Supports a Rank 4 Classification: Structural and neurological findings are recorded under the STRUCTURAL and NEUROLOGICAL headings of the Brain section (page 3) of the FASD Diagnostic Form. A 'Severity Score' is provided along the left margin of the Form to allow the clinical team to rank the severity of all structural and neurological findings. Only structural and/or neurological findings that receive a Severity Score = 3 (Significant) can contribute toward a Brain Rank 4 classification. For example, a seizure disorder not due to a postnatal insult would receive a Severity Score = 3. Often this type of seizure would warrant medical treatment. A seizure that occurred just once during a high fever would receive a Severity Score = 2. Absence of any seizure-like activity would receive a Severity Score = 1. An OFC $\leq$ -2 SDs ($\leq 3^{rd}$ percentile) would receive a Severity Score = 3. An OFC > 3^{rd} percentile and $\leq 10^{th}$ percentile would receive a Severity Score = 2. An OFC > 10^{th} percentile would receive a Severity Score = 1. This Severity Score allows one to rapidly scan the FASD Diagnostic Form and identify significant findings that support a Rank 4 classification.

Brain Rank 3: (Severe Dysfunction) "Static Encephalopathy"
"Probable" Evidence of Brain Damage.

Rank 3 Description: Brain Rank 3 is assigned when a patient presents with severe brain dysfunction. These patients typically have challenges across multiple domains of function that may include, but are not limited to, executive function, memory, cognition, processing speed, academic achievement, language, motor, sensory, attention or activity level.

Rank 3 Criteria: Brain Rank 3 is assigned when there is evidence of "severe" impairment in 3 or more domains of brain function. "Sever" impairment is defined as performance 2 or more standard deviations below the mean (or its equivalent) on standardized, validated neuropsychological assessment tools (e.g., WISC, WIAT, CELF, D-KEFS, NEPSY, CVLT, VMI, etc.) administered and interpreted by qualified professionals (e.g., psychologists, occupational therapists, speech-language pathologists, etc). Developmental instruments, such as the Bayley Scales of Infant Development would typically not be used as a source of psychometric data to support a classification of severe brain dysfunction because developmental delay is not always predictive of underlying brain damage/dysfunction. The one exception to this rule would be developmental scores that reflect global developmental delay.

Documenting the Evidence that Supports a Rank 3 Classification*:* The clinical team records which functional domains are impaired and which tests/scores support their decisions on the Functional Domains page (page 7) of the FASD Diagnostic Form. Evidence to support a Rank 3 classification must come from standardized psychometric tests administered by professionals. The outcomes of these psychometric tests are recorded on pages 3-5 of the FASD Diagnostic Form. A 'Severity Score' is provided along the left margin of the Functional Domains page (page 7) to allow the clinical team to rank the severity of delay/impairment for each assessed domain. A functional domain must receive a Severity Score = 3 (Severe) to contribute toward a Brain Rank 3 classification. The Severity Score is described more fully below.

Brain Rank 2 (Moderate Delay/Dysfunction). "Neurodevelopmental Disorder (or Delay)" "Possible" Evidence of Brain Damage.

Rank 2 Description: This Rank should be given to two groups of patients, all of whom should have histories of behavioral, cognitive, and/or developmental problems.

One group includes infants/toddlers/young children (generally under 7 years of age) who are not developmentally mature enough to engage in assessments of higher order functions such as executive function, memory, higher order language skills. If a child is under 7-8 years of age at the time of assessment, they should be reassessed at 9 years of age when their brains are sufficiently mature to engage in assessment of higher order functions. *Note the term "neurodevelopmental disorder" is assigned to brain Rank 2. When this Rank is being assigned to infants/toddlers based primarily on developmental data, the clinical team may decide to replace the term "neurodevelopmental disorder" with "neurodevelopmental delay".*

The other group of patients is those whose testing did not reveal 3 domains of function 2 or more standard deviations below the mean required for a Rank 3 classification, but moderate to less severe impairments were identified nonetheless, preventing them from being classified Brain Rank 1 (normal function).

***Rank 2 Criteria*:** Rank 2 reflects a range of delay and/or dysfunction that suggests the possibility of underlying brain damage. At the mild end of the Rank 2 range are those who present with developmental delay that, by clinical judgment, precludes a Rank 1 classification and warrants intervention. At the severe end of the Rank 2 range are those who present with 1 or 2 domains of function 2 or more standard deviations below the mean, with multiple domains 1.5 standard deviations below the mean (Table 5). A Rank 2, by definition, is assigned to all who fall between Ranks 1 and 3. Evidence to support a Rank 2 classification can come from standardized psychometric tests, observational data, and/or caregiver interview. Deficiencies (or definite differences from normative expectations) recorded in the FUNCTIONAL section (pages 3-7) of the FASD Diagnostic Form serve to support a Rank 2 classification.

Documenting the Evidence that Supports a Rank 2 Classification: The clinical team records which functional domains are delayed or impaired and which tests/scores support their decisions on the Functional Domains page (page 7) of the FASD Diagnostic Form. Evidence to support a Rank 2 classification can come from standardized psychometric tests, observational data, and/or caregiver interview. These data are recorded on pages 3-6 of the FASD Diagnostic Form. A

'Severity Score' is provided along the left margin of the Functional Domains page (page 7) to allow the clinical team to rank the severity of delay or impairment for each assessed domain. Typically a patient that meets the criteria for Rank 2 will have at least one domain with a Severity Score = 2 (mild to moderate delay or impairment), but less than three domains with a Severity Score = 3 (severe impairment). The Severity Score is described more fully below.

Brain Rank 1 (No Current Evidence of Delay/Dysfunction)
"No" Current Evidence of Brain Damage.

A Rank 1 classification is assigned when no functional or developmental problems are discerned that are likely to reflect brain damage and no intervention recommendations are warranted. Evidence to support a Rank 1 can come from standardized psychometric tests, observational data, and/or caregiver interview. While this classification is typically quite rare in an FASD Diagnostic Clinic, it might help to think of this outcome in the context of a well-child assessment conducted in a general pediatric clinic where most children would be classified as Rank 1. On the other hand, if patients under 3 years of age with prenatal alcohol exposure present with normal development (Brain Rank 1) it would be important to conduct a re-evaluation later in childhood when they are old enough to engage in more sophisticated assessments of brain function. The neurodevelopmental impairments caused by prenatal alcohol exposure often do not fully manifest until later in childhood (Pruner et al., 2024). Infants/toddlers with prenatal alcohol exposure at greatest risk of severe brain dysfunction that will not manifest until later in childhood are those presenting with any of the sentinel physical features of FASD (growth deficiency, FAS facial features or microcephaly) (Astley et al., 2016).

Completing the Brain Section of the FASD Diagnostic Form

The Brain section appears on pages 3 through 7 of the FASD Diagnostic Form. These pages serve as a place to record pertinent structural, neurological, neuropsychological, and caregiver interview data available on the patient. Although space has been provided to record a full complement of assessments, we are not implying that all these assessments must be conducted to derive a diagnosis. It is the responsibility of the clinical team to select the most appropriate assessment battery for an individual patient. Recording data for the structural, neurological, and neuropsychological sections is self-explanatory. The Caregiver Interview section, however, warrants further explanation.

An important aspect of the FASD evaluation is an in-depth interview of the caregivers of the patient. This interview takes approximately one hour and is conducted by a qualified member(s) of the clinical team. At the University of Washington FASDPN clinic, this interview is conducted by the medical doctor while the patient is being formally assessed by the other clinical team members. As in any diagnostic situation, once records are reviewed and there is a preliminary case formulation, the diagnostic interview will address several questions, such as: What are the problems that led to the diagnostic referral? What do the caregivers hope to gain from the assessment? What are the caregivers' views of the patient's overall strengths and weaknesses? What is the child's social and medical history pertinent to this diagnostic evaluation? In an FASD diagnostic evaluation, we have found it very useful to also methodically ask questions that review age-appropriate functional abilities in areas that, according to the literature, are commonly problematic for alcohol-exposed individuals. These areas (planning/temporal skills, behavioral regulation/sensory motor integration,

abstract thinking/judgment, memory/learning/information processing, spatial skills/spatial memory, social skills/adaptive behavior, and motor/oral motor control) are presented on the FASD Diagnostic Form (page 6). Routinely inquiring about the patient's capabilities in these areas serves several purposes. First, the caregivers' answers to these questions give insight into their interpretation of the patient's behaviors and about their general relationship with the patient. Second, it is often helpful to compare this subjective assessment to the psychometric profile. This can reveal information about the pattern of neurodevelopmental difficulties that standardized testing may miss or provide evidence that is supportive of test results. The data recorded on page 6 of the Diagnostic Form are non-standardized observational measures. A summary of the first 1,400 caregiver interviews at the FASDPN clinic documented caregivers perceptions of their child's strengths and challenges were remarkably concordant with their child's neuropsychological test outcomes and FASD diagnostic classification (Astley, 2013; see Fig. 19).

Severity Score [0, 1, 2, 3]

Along the left margin of each Brain page is a Severity Score. This Severity Score serves two purposes. 1) It allows one to rapidly scan the left margin of the Brain pages to see what structural, neurological, and functional areas are most impacted. 2) The Severity Scores in the Structural/Neurological Sections and the Functional Domains page also serve to document what evidence was present to meet the criteria for Brain Ranks 2, 3, and 4, as described above. For example, at least one area in the Structural or Neurological Sections should have a Severity Score = 3 to meet criteria for a Brain Rank 4. At least three domains on the Functional Domains page should a Severity Score = 3 to meet criteria for a Brain Rank 3.

The clinical team ranks the level of impairment/abnormality as follows:

0	Unknown, Not Assessed
1	Within Normal Limits
2	Mild to Moderate
3	Severe

For outcomes measured on standardized scales, in general, outcomes two or more standard deviations below the norm would be judged severe, whereas outcomes between one and two standard deviations below the norm could be judged mild to moderate.

A comprehensive assessment will identify domains of strength, as well as domains with mild to severe impairment. Documenting the outcomes of all assessed domains, not just those with severe impairment, is important for treatment planning.

Primary Sources of Information Used and Generated by the Interdisciplinary Team to Derive the Brain Rank.

1. **Previous medical, school, psychological and mental health assessments**.

   Prior to the diagnostic evaluation, consent is obtained from the legal guardian to obtain the results of prior school, psychological and/or medical assessments that will be pertinent to the diagnostic evaluation. These assessments typically include:

   A. Medical records (growth, neurological evaluations, brain imaging, other medical conditions).
   B. School records (IEP, school psychological and/or achievement assessments).
   C. Psychological Records (neuropsychological assessments).
   D. Mental Health Records (mental health assessments, diagnoses, medications).

   These records are reviewed and discussed by the interdisciplinary team prior to the diagnostic evaluation.

2. **Caregiver interview conducted at the time of the diagnostic evaluation**.

   As described above, a semi-structured interview (page 6 of the *FASD Diagnostic Form*) is conducted with the caregiver(s) to document their concerns, impressions and experiences with the patient.

3. **Psychometric assessments conducted at the time of, or in preparation for, the diagnostic evaluation.**

   The primary goal in the diagnostic evaluation is to document/verify the presence of brain abnormalities. The battery of assessments administered by the interdisciplinary team will most likely differ for each patient. Assessments will be selected based on the patient's age and area(s) of perceived deficit. Many patients will have already had some level of prior assessment conducted by other educational and health care providers. Thus, assessments conducted by the interdisciplinary diagnostic team will be selected to compliment, not duplicate what has already been done. The FASDPN Psychometric and Behavior Observations Training Guide (Olson et al., 2005) provides a brief overview of psychometric assessments typically used to assess patients of all ages seen in the FASDPN clinics. Clarren et al., 2000 provides a description of a typical FASD interdisciplinary diagnostic evaluation at the University of Washington FASDPN clinic. The following published research reports document the neuropsychological, behavioral, sensory, sleep disorder, and psychiatric outcomes of individuals across the spectrum of FASD (Astley, 2010; Astley et al., 2009a; Chen et al., 2012; Franklin et al., 2008; Jirikowic et al., 2008; Jirikowic et al., 2008a; Jirikowic et al., 2013; Olson et al., 2007).

Table 5: Criteria for Brain Ranks 1 through 4

4-Digit Diagnostic Brain Rank*	Probability of underlying Brain Damage	Confirmatory Findings
4	Definite **Structural and/or Neurological Abnormalities** *Static Encephalopathy*	● Microcephaly: OFC 2 or more SDs below the norm. *and / or* ● Significant abnormalities in brain structure of presumed prenatal origin. *and / or* ● Evidence of abnormal neurological findings (e.g. seizures, tick disorders, etc.) likely to be of prenatal origin.
3	Probable **Severe Dysfunction** *Static Encephalopathy*	● Severe impairment (2 or more SDs below the mean) in 3 or more domains of brain function such as, but not limited to: cognition, achievement, memory, executive function, motor, sensory, language, attention, activity level, neurological 'soft' signs.
2	Possible **Moderate Dysfunction** *Neurodevelopmental Disorder*	● Evidence of delay or dysfunction that do not permit a Rank 1 classification, but also do not permit a Rank 3 classification.
1	Unlikely **No Dysfunction**	● No current evidence of delay or dysfunction likely to reflect brain damage.

* Transfer the resulting 4-Digit Diagnostic Rank for Brain to the 4-Digit Diagnostic Code Grid on page 1 of the FASD Diagnostic Form (Section II).

FASD 4-Digit Code

3

Rank	Growth	Face	Brain	Prenatal Alcohol	Other Prenatal Risks	Other Postnatal Risks
4	severe	all 3 features	abnormal structure/neurology	high	high	high
3	moderate	2.5 features	severe dysfunction	some	some	some
2	mild	1-2 features	moderate dysfunction	unknown	unknown	unknown
1	normal	no features	normal function	none	none	none

III. Instructions for Deriving the 4-Digit Code

B.4. Ranking Prenatal Alcohol Exposure

Method for Ranking Alcohol: The 4th Digit of the 4-Digit Diagnostic Code

Alcohol exposure is ranked according to the quantity, timing, frequency, and certainty of exposure during pregnancy (Table 6). The case-definitions for the four Ranks address two important issues: 1) that exposure information in a clinical setting can be of limited availability or of unknown accuracy (Astley, 2013; Astley et al, 2019) and 2) and a clear consensus is not available concerning the amount of alcohol that can actually be toxic to each individual fetus (Stratton et al., 1996; (Astley)Hemingway et al., 2019a).

The case-definitions for prenatal alcohol exposure differentiate four clinically meaningful groups: Rank 4: confirmed exposure to high levels of alcohol; Rank 3: confirmed exposure, but the level is less than Rank 4 or the level is unknown; Rank 2: unknown exposure (neither confirmed absent nor confirmed present); and Rank 1: confirmed absence of exposure from conception to birth. These exposure Ranks are based on verbal or written records. High exposure is defined generally to be a blood alcohol concentration of greater than 100 mg/dL (a level that typically can be reached by a 55-kg woman consuming six to eight beers) weekly, early in pregnancy. In the absence of a clear consensus on the amount of alcohol that can actually be toxic to the fetus, this general definition should only serve as a guide, not a threshold.

One example of a 'Rank 4' exposure is the birth mother reported drinking to the point of intoxication weekly throughout pregnancy. Two examples of 'Rank 3' exposures include: 1) birth mother was observed to be drinking during pregnancy, but the amount is unknown, 2) birth mother reported drinking a single glass of wine weekly, but stopped drinking as soon as she learned she was pregnant at 2 months. Two examples of when alcohol exposure is ultimately unknown and thus coded as Rank 2 include: 1) the child is adopted and the birth records are closed, and 2) the birth mother is known to have a problem with drinking, but there are no records or direct observation of her drinking during the index pregnancy. A Rank 1 classification (confirmed absence of drinking from conception to birth) may not be as common as one would hope in the general population. Most women of reproductive age consume some level of alcohol and not all pregnancies are planned.

The Rank 4 FAS facial phenotype as defined by the 4-Digit Code can be used to confirm prenatal alcohol exposure when a written or verbal history of prenatal alcohol exposure is unknown (Alcohol Rank 2). The 4-Digit Code Rank 4 FAS facial phenotype is the only facial phenotype, to date, that provides sufficient positive predictive value (PPV) and specificity (100%) to prenatal alcohol exposure to allow the facial phenotype to serve as confirmation of alcohol exposure in a diagnostic setting when a verbal or written record of prenatal alcohol exposure is unavailable. Even minimal relaxation of the phenotype (e.g., Face Rank 3) results in PPV (35%) and specificity (88.7%) values too low to use as confirmation of prenatal alcohol exposure. (Astley & Clarren, 1996, 2000, 2001; (Astley)Hemingway et al., 2020). If the facial phenotype of FAS can only be caused by prenatal alcohol exposure, the following two conditions should hold true: 1) All individuals with the FAS facial phenotype have prenatal alcohol exposure (100% PPV); and 2) No individual with a confirmed absence of prenatal alcohol exposure will have the FAS facial phenotype (100% specificity). Data to date documents the Rank 4 FAS facial phenotype meets these two conditions ((Astley)Hemingway et al.,

2020). The Rank 4 FAS facial phenotype can also be used to confirm an individual's prenatal alcohol exposure adversely impacted their fetal development.

Table 6: Criteria for Prenatal Alcohol Exposure Ranks 1 through 4

4-Digit Diagnostic Rank	Prenatal Alcohol Exposure Category	Description of Alcohol Use During Pregnancy
4	High Risk	• Alcohol use during pregnancy is CONFIRMED. *and* • Reported exposure pattern is consistent with the medical literature placing the fetus at "high risk" (generally high peak blood alcohol concentrations delivered at least weekly in early pregnancy, reports of intoxication, binge drinking).
3	Some Risk	• Alcohol use during pregnancy is CONFIRMED. *and* • Level of alcohol use is reported to be less than Rank (4) or level is unknown.
2	Unknown Risk	• Alcohol use during pregnancy is UNKNOWN (neither confirmed absent nor confirmed present).
1	No Risk	• Alcohol use during pregnancy is CONFIRMED ABSENT from conception to birth.

Transfer the resulting 4-Digit Diagnostic Rank for Alcohol Exposure to the 4-Digit Diagnostic Code Grid on page 1 of the FASD Diagnostic Form (Section II).

FASD 4-Digit Code

Rank	Growth	Face	Brain	Prenatal Alcohol (4)	Other Prenatal Risks	Other Postnatal Risks
4	severe	all 3 features	abnormal structure/neurology	high	high	high
3	moderate	2.5 features	severe dysfunction	some	some	some
2	mild	1-2 features	moderate dysfunction	unknown	unknown	unknown
1	normal	no features	normal function	none	none	none

III. Instructions for Deriving the 4-Digit

B.5. Ranking Other Pre- and Postnatal Risk Factors

The Importance of Documenting Other Risk Factors

A comprehensive diagnostic process must take into consideration all other adverse prenatal and postnatal adverse exposures and experiences, not just prenatal alcohol exposure. Many of the outcomes observed in individuals with prenatal alcohol exposure are not specific to (caused only by) prenatal alcohol exposure. A variety of other prenatal (poor prenatal care, pregnancy complications, familial genetics, and exposure to other potentially teratogenic agents, etc.), and/or postnatal (physical/sexual abuse, neglect, disrupted placement histories, trauma, head injuries, chronic substance abuse by the patient, etc.) risk factors could also contribute to the adverse outcomes presented by the patient. In the FASDPN clinical population, other prenatal and postnatal risk factors were 3 to 7-fold more prevalent than in the general population (Astley Hemingway et al., 2020).

The 4-Digit Diagnostic method requires the clinical team to record all pertinent prenatal and postnatal risk factors on the standardized FASD Diagnostic Form, rank their severity of risk on 4-point Likert scales, report them in the medical summary, and take them into consideration when deriving a diagnosis and intervention plan.

It is important to note that the presence of other risk factors does not reduce the teratogenic potential of alcohol. When multiple risk factors are present, including prenatal alcohol exposure, each risk factor has the potential of being fully responsible, partially responsible, or not responsible at all for any one particular outcome. Together these risk factors can have additive or multiplicative adverse impacts on development.

While there is currently no medical means to determine which risk factor is responsible for which outcome in an individual patient, group statistics can begin to shed light on this issue. A recent study addressed the question "*What proportion of brain structural and functional abnormalities observed among children with FASD is explained by their prenatal alcohol exposure and their other prenatal and postnatal risks*? (Astley Hemingway et al., 2020). The study revealed prenatal alcohol exposure was the dominant risk factor explaining the largest proportion of variance (52%) in regional brain size (total brain, frontal lobe, caudate, hippocampus and corpus callosum) and brain function (intellect, achievement, memory, language, executive-function, motor, adaptation, behavior-attention and mental health symptoms). Other prenatal and postnatal risk factors were 3 to 7-fold more prevalent among these children with FASD than documented in the general population. Individually, each risk factor explained a statistically significant, but smaller proportion of variance (5-15%) in brain outcome compared to prenatal alcohol exposure. In combination, the proportion of variance explained by the presence of multiple prenatal and postnatal risks rivaled that of prenatal alcohol exposure.

A. Other Prenatal Risk Factors: Rank Definitions

Prenatal exposures and experiences are recorded and assigned a Rank on page 9 of the Diagnostic Form. The definitions below are intended to provide guidance for ranking. The circumstances surrounding each patient case will be unique. Selecting a rank will require clinical judgement.

Rank 4: High Risk

This Rank is reserved for alternate genetic conditions (e.g., Fragile X, velocardiofacial syndrome, down syndrome, etc.) or exposure to known teratogens (e.g., dilantin, valproic acid, etc.) that have been clearly shown to produce physical abnormalities.

Rank 3: Some Risk

This category is used for potential genetic conditions, exposures or prenatal conditions that have been associated with physical or neurodevelopmental problems in a less well-established way, when compared to those falling in Prenatal Rank 4. Examples of conditions that would be placed in this category could include poor prenatal care; patients whose parents have attention deficit disorders, significant learning disabilities or learning problems thought to be due to a non-specific (and non-teratogenic) source; prenatal exposure to non-teratogenic drugs like marijuana; and cigarette smoking during pregnancy.

Rank 2: Unknown Risk

This category is used when the details of the family background and gestation are unknown – generally in the circumstance of a closed adoption.

Rank 1: No Known Risk

On occasion, the genetic, teratogenic, and prenatal histories are well documented and no factors can be identified that would explain the abnormalities found in the patient.

B. Postnatal Risk Factors: Rank Definitions

Postnatal risks are recorded and assigned a Rank on page 9 of the Diagnostic Form.

There is a growing body of literature on the prevalence and impact of traumatic childhood experiences among individuals with prenatal alcohol exposure (Price et al., 2017; (Astley) Hemingway SJA et al., 2020; Lebel et al., 2019: Rockhold et al., 2023). Documenting postnatal adverse experiences can be achieved retrospectively from historical records and/or prospectively from administration of parent-report questionnaires like the Adverse Childhood Experiences (ACES) (Felitti et al., 1998) or the Traumatic Events Screening Inventory (TESI) (Ghosh-Ippen et al., 2002).

Childhood adversity has been conceptualized variously as linking specific experiences with outcomes, cumulative risk (e.g. ACE score), dimensional approaches (threat / deprivation / unpredictability frameworks), and "topological" models which consider features like chronicity, intensity, and developmental timing of adversity along with child aspects like stress response phenotypes and environmental factors such as predictability and caregiver responses (Ellis et al., 2022; Rockhold et al., 2023; Gabard-Durnam & McLaughlin, 2020; Smith & Polak, 2021).

Until there is more empirical support for one of these approaches, we rely upon clinical judgement to rank the magnitude of risk posed by the adverse postnatal experiences and the likelihood that postnatal events contributed to growth and developmental differences. The definitions provided below are meant to provide guidance. Consider factors like severity, chronicity, number of risk factors, timing (e.g. developmentally sensitive period of the first 2-3 years or recency), child's perceptions of the events, and buffering by caregivers (resilience/resources or lack thereof) when evaluating the degree of adversity and how likely the postnatal environment is to have influenced the patient's outcomes.

Rank 4: High Risk

This Rank is used to note postnatal circumstances that have been shown to have a significant adverse effect on development in most instances. Examples include, but are not limited to, physical and/or sexual abuse, multiple disrupted placements with clear impact on the child, severe neglect (based on clinical judgment or apparent impacts such as failure to thrive), serious head injury, or medical conditions which lead to brain impacts (e.g., hypoxic/ischemic encephalopathy, kernicterus, severe malnutrition). Perinatal/prematurity factors like extremely low birth weight (ELBW), extremely premature (< 28 weeks), and intracranial hemorrhage grade 3-4 can be captured here as well). Other postnatal experiences that could contribute to a high-risk Rank 4 classification are presented on page 9 of the Diagnostic Form (page 16 of this Diagnostic Guide).

Rank 3: Some Risk

This Rank is used to note conditions akin to those in Rank 4, but the circumstances are judged less severe and so less likely to be a definite factor in the patient's present condition. Obviously, clinical judgment is needed in judging the magnitude of postnatal problems and interpreting this information into a Rank 3 or 4 placement.

Rank 2: Unknown Risk

This Rank is used when historical information is missing. This is sometimes the case with adopted children or those in foster care. Adult patients may, at times, be unable to reconstruct their own early histories.

Rank 1: No Known Risk

This Rank is used when a well-documented history confirms an absence of adverse postnatal exposures/events.

Transfer the resulting 4-Digit Diagnostic Ranks for Prenatal and Postnatal Risks to the 4-Digit Diagnostic Code Grid on page 1 of the FASD Diagnostic Form in Section II.

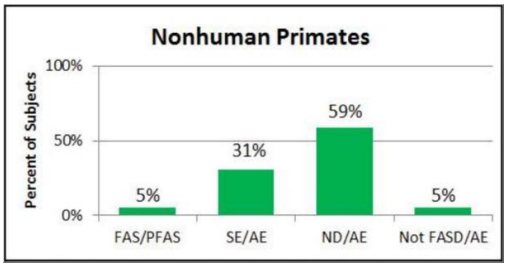
FASD 4-Digit Code

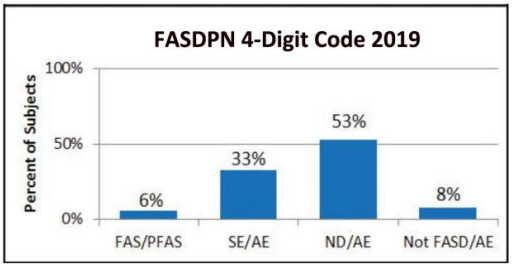
Rank	Growth	Face	Brain	Prenatal Alcohol	Other Prenatal Risks (3)	Other Postnatal Risks (4)
4	severe	all 3 features	abnormal structure/neurology	high	high	high
3	moderate	2.5 features	severe dysfunction	some	some	some
2	mild	1-2 features	moderate dysfunction	unknown	unknown	unknown
1	normal	no features	normal function	none	none	none

IV. Diagnostic Categories

Generic descriptions for each of the 19 Diagnostic Categories are presented on the following pages listed alphabetically from A through S. A complete list of the 19 categories is presented in Section IV. Note only 6 of the Diagnostic Categories (A-E and 4 codes in J highlighted in red) fall "broadly" under the umbrella of FASD in accordance with the 4-Digit Code. What do we mean by "broadly" under the umbrella of FASD?

Fetal Alcohol Spectrum Disorders are, by definition, adverse outcomes *caused* by prenatal alcohol exposure. When we label a diagnosis FAS, we are stating explicitly that alcohol caused the syndrome. *How do we know an individual's prenatal alcohol exposure caused their FAS?* FAS is characterized by growth deficiency, brain abnormalities and the FAS facial phenotype. Although a myriad of prenatal and postnatal risk factors including PAE can cause adverse growth and brain outcomes, only prenatal alcohol exposure can cause the FAS facial phenotype. But the diagnoses SE/AE and ND/AE do not require the FAS facial phenotype. *Do all individuals with SE/AE and ND/AE have FASD?* Not necessarily. Only the subset of individuals whose growth and/or brain impairments were caused (in whole or in part) by their prenatal alcohol exposure. Which subset of individuals is that? We currently have no way of knowing. Individuals with SE and ND caused by their alcohol exposure have FASD. Individuals with SE/AE and ND/AE that was not caused by their alcohol exposure do not have FASD. *What proportion of individuals with SE/AE or ND/AE have FASD?* Research to date would suggest it is likely the majority. Although the prevalence of other prenatal and postnatal risk factors is 3- to 7-fold higher in the FASDPN clinic population than in the general population, a recent study ((Astley) Hemingway et al., 2020) found among these children with prenatal alcohol exposure and other risk factors, alcohol was the dominant risk factor explaining the largest proportion (50%) of variance in regional brain size and brain function. Individually, each of the other risk factors explained a smaller proportion of the variance, but in combination explained an additional 20-30% of the variance. *What would the prevalence of FAS, SE/AE and ND/AE look like if alcohol was the only risk factor?* The 4-Digit Code was applied to a nonhuman primate model of FASD where the only risk factor was PAE ((Astley) Hemingway et al., 2019). The prevalence of the FAS, SE/AE and ND/AE caused by alcohol looked near identical to the prevalence of FASD diagnostic outcomes observed among 3,000 patients with prenatal alcohol exposure evaluated in the FASDPN over 30 years.





The 256 Diagnostic Codes can be logically grouped into 19 Diagnostic Categories.

Only the 5 Categories in red font (A-E) and 4 codes in Category J with the Rank 4 facial phenotype are considered to be broadly under the umbrella of FASD in accordance with the 4-Digit Code.

Category	Name
A	Fetal alcohol syndrome
B	Sentinel physical finding(s) / static encephalopathy / alcohol exposed
C	Static encephalopathy / alcohol exposed
D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
E	Neurodevelopmental disorder / alcohol exposed
F	Sentinel physical finding(s) / alcohol exposed
G	No sentinel physical findings or brain abnormalities detected / alcohol exposed
H	Sentinel physical finding(s) / static encephalopathy / alcohol exposure unknown
I	Static encephalopathy / alcohol exposure unknown
J	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposure unknown)
K	Neurodevelopmental disorder / alcohol exposure unknown
L	Sentinel physical finding(s) / alcohol exposure unknown
M	No sentinel physical findings or brain abnormalities detected / alcohol exposure unknown
N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
O	Static encephalopathy / no alcohol exposure
P	Sentinel physical finding(s) / neurodevelopmental disorder / no alcohol exposure
Q	Neurodevelopmental disorder / no alcohol exposure
R	Sentinel physical finding(s) / no alcohol exposure
S	No sentinel physical findings or brain abnormalities detected / no alcohol exposure

V. 4-Digit Diagnostic Codes Within each Diagnostic Category

Only the 4-Digit Codes in red font are considered to be broadly under the umbrella of FASD in accordance with the 4-Digit Code.

Category	Diagnostic Name and Codes
A	Fetal alcohol syndrome
	1333 1433 2333 2433 3333 3433 4333 4433
	1334 1434 2334 2434 3334 3434 4334 4434
	1343 1443 2343 2443 3343 3443 4343 4443
	1344 1444 2344 2444 3344 3444 4344 4444
	1432 2432 3432 4432 1442 2442 3442 4442
B	Sentinel physical finding(s) / static encephalopathy / alcohol exposed
	3133 3233 4133 4233
	3134 3234 4134 4234
	3143 3243 4143 4243
	3144 3244 4144 4244
C	Static encephalopathy / alcohol exposed
	1133 1233 2133 2233
	1134 1234 2134 2234
	1143 1243 2143 2243
	1144 1244 2144 2244
D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
	1323 2323 3123 3323 4123 4323
	1324 2324 3124 3324 4124 4324
	1423 2423 3223 3423 4223 4423
	1424 2424 3224 3424 4224 4424
E	Neurodevelopmental disorder / alcohol exposed
	1123 1223 2123 2223
	1124 1224 2124 2224

Category	Diagnostic Name and Codes (4-Digit Codes under the umbrella of FASD in red font)
F	Sentinel physical finding(s) / alcohol exposed 1313 2313 3113 3313 4113 4313 1314 2314 3114 3314 4114 4314 1413 2413 3213 3413 4213 4413 1414 2414 3214 3414 4214 4414
G	No physical findings or brain abnormalities detected / alcohol exposed 1113 1213 2113 2213 1114 1214 2114 2214
H	Sentinel physical finding(s) / static encephalopathy / alcohol exposure unknown 1332 2332 3132 3232 3332 4132 4232 4332 1342 2342 3142 3242 3342 4142 4242 4342
I	Static encephalopathy / alcohol exposure unknown 1132 1232 2132 2232 1142 1242 2142 2242
J	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposure unknown 1322 2322 3122 3322 4122 4322 1422 2422 3222 3422 4222 4422
K	Neurodevelopmental disorder / alcohol exposure unknown 1122 1222 2122 2222
L	Sentinel physical finding(s) / alcohol exposure unknown 1312 2312 3112 3312 4112 4312 1412 2412 3212 3412 4212 4412
M	No physical findings or brain abnormalities detected / alcohol exposure unknown 1112 2112 1212 2212

Category	Diagnostic Name and Codes
N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure 1331 2331 3131 3331 4131 4331 1341 2341 3141 3341 4141 4341 1431 2431 3231 3431 4231 4431 1441 2441 3241 3441 4241 4441
O	Static encephalopathy / no alcohol exposure 1131 1231 2131 2231 1141 1241 2141 2241
P	Sentinel physical finding(s) / neurodevelopmental disorder / no alcohol exposure 1321 2321 3121 3321 4121 4321 1421 2421 3221 3421 4221 4421
Q	Neurodevelopmental disorder / no alcohol exposure 1121 2121 2221 1221
R	Sentinel physical finding(s) / no alcohol exposure 1311 2311 3111 3311 4111 4311 1411 2411 3211 3411 4211 4411
S	No physical findings or brain abnormalities detected / no alcohol exposure 1111 2111 1211 2211

VI. 4-Digit Diagnostic Codes Sorted Numerically

Code	Category	Diagnostic Name (4-Digit Codes under the umbrella of FASD in red font)
1111	S	No sentinel physical findings or brain abnormalities detected / no alcohol exposure
1112	M	No sentinel physical findings or brain abnormalities detected / alcohol exposure unknown
1113	G	No sentinel physical findings or brain abnormalities detected / alcohol exposure
1114	G	No sentinel physical findings or brain abnormalities detected / alcohol exposure
1121	Q	Neurodevelopmental disorder / no alcohol exposure
1122	K	Neurodevelopmental disorder / alcohol exposure unknown
1123	E	Neurodevelopmental disorder / alcohol exposed
1124	E	Neurodevelopmental disorder / alcohol exposed
1131	O	Static encephalopathy / no alcohol exposure
1132	I	Static encephalopathy / alcohol exposure unknown
1133	C	Static encephalopathy / alcohol exposed
1134	C	Static encephalopathy / alcohol exposed
1141	O	Static encephalopathy / no alcohol exposure
1142	I	Static encephalopathy / alcohol exposure unknown
1143	C	Static encephalopathy / alcohol exposed
1144	C	Static encephalopathy / alcohol exposed
1211	S	No sentinel physical findings or brain abnormalities detected / no alcohol exposure
1212	M	No sentinel physical findings or brain abnormalities detected / alcohol exposure unknown
1213	G	No sentinel physical findings or brain abnormalities detected / alcohol exposure
1214	G	No sentinel physical findings or brain abnormalities detected / alcohol exposure
1221	Q	Neurodevelopmental disorder / no alcohol exposure
1222	K	Neurodevelopmental disorder / alcohol exposure unknown
1223	E	Neurodevelopmental disorder / alcohol exposed
1224	E	Neurodevelopmental disorder / alcohol exposed
1231	O	Static encephalopathy / no alcohol exposure
1232	I	Static encephalopathy / alcohol exposure unknown
1233	C	Static encephalopathy / alcohol exposed
1234	C	Static encephalopathy / alcohol exposed
1241	O	Static encephalopathy / no alcohol exposure
1242	I	Static encephalopathy / alcohol exposure unknown
1243	C	Static encephalopathy / alcohol exposed
1244	C	Static encephalopathy / alcohol exposed
1311	R	Sentinel physical finding(s) / no alcohol exposure
1312	L	Sentinel physical finding(s) / alcohol exposure unknown
1313	F	Sentinel physical finding(s) / alcohol exposed
1314	F	Sentinel physical finding(s) / alcohol exposed
1321	P	Sentinel physical finding(s) / neurodevelopmental disorder / no alcohol exposure
1322	J	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposure unknown
1323	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed

Code	Category	Diagnostic Name (4-Digit Codes under the umbrella of FASD in red font)
1324	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
1331	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
1332	H	Sentinel physical finding(s) / static encephalopathy / alcohol exposure unknown
1333	A	FAS
1334	A	FAS
1341	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
1342	H	Sentinel physical finding(s) / static encephalopathy / alcohol exposure unknown
1343	A	FAS
1344	A	FAS
1411	R	Sentinel physical finding(s) / no alcohol exposure
1412	L	Sentinel physical finding(s) / alcohol exposure unknown
1413	F	Sentinel physical finding(s) / alcohol exposed
1414	F	Sentinel physical finding(s) / alcohol exposed
1421	P	Sentinel physical finding(s) / neurodevelopmental disorder / no alcohol exposure
1422	J	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposure unknown
1423	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
1424	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
1431	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
1432	A	FAS
1433	A	FAS
1434	A	FAS
1441	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
1442	A	FAS
1443	A	FAS
1444	A	FAS
2111	S	No sentinel physical findings or brain abnormalities detected / no alcohol exposure
2112	M	No sentinel physical findings or brain abnormalities detected / alcohol exposure unknown
2113	G	No sentinel physical findings or brain abnormalities detected / alcohol exposure
2114	G	No sentinel physical findings or brain abnormalities detected / alcohol exposure
2121	Q	Neurodevelopmental disorder / no alcohol exposure
2122	K	Neurodevelopmental disorder / alcohol exposure unknown
2123	E	Neurodevelopmental disorder / alcohol exposed
2124	E	Neurodevelopmental disorder / alcohol exposed
2131	O	Static encephalopathy / no alcohol exposure
2132	I	Static encephalopathy / alcohol exposure unknown
2133	C	Static encephalopathy / alcohol exposed
2134	C	Static encephalopathy / alcohol exposed
2141	O	Static encephalopathy / no alcohol exposure
2142	I	Static encephalopathy / alcohol exposure unknown
2143	C	Static encephalopathy / alcohol exposed
2144	C	Static encephalopathy / alcohol exposed)
2211	S	No sentinel physical findings or brain abnormalities detected / no alcohol exposure
2212	M	No sentinel physical findings or brain abnormalities detected / alcohol exposure unknown
2213	G	No sentinel physical findings or brain abnormalities detected / alcohol exposure

Code	Category	Diagnostic Name (4-Digit Codes under the umbrella of FASD in red font)
2214	G	No sentinel physical findings or brain abnormalities detected / alcohol exposure
2221	Q	Neurodevelopmental disorder / no alcohol exposure
2222	K	Neurodevelopmental disorder / alcohol exposure unknown
2223	E	Neurodevelopmental disorder / alcohol exposed
2224	E	Neurodevelopmental disorder / alcohol exposed
2231	O	Static encephalopathy / no alcohol exposure
2232	I	Static encephalopathy / alcohol exposure unknown
2233	C	Static encephalopathy / alcohol exposed
2234	C	Static encephalopathy / alcohol exposed
2241	O	Static encephalopathy / no alcohol exposure
2242	I	Static encephalopathy / alcohol exposure unknown
2243	C	Static encephalopathy / alcohol exposed
2244	C	Static encephalopathy / alcohol exposed
2311	R	Sentinel physical finding(s) / no alcohol exposure
2312	L	Sentinel physical finding(s) / alcohol exposure unknown
2313	F	Sentinel physical finding(s) / alcohol exposed
2314	F	Sentinel physical finding(s) / alcohol exposed
2321	P	Sentinel physical finding(s) / neurodevelopmental disorder / no alcohol exposure
2322	J	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposure unknown
2323	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
2324	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
2331	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
2332	H	Sentinel physical finding(s) / static encephalopathy / alcohol exposure unknown
2333	A	FAS
2334	A	FAS
2341	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
2342	H	Sentinel physical finding(s) / static encephalopathy / alcohol exposure unknown
2343	A	FAS
2344	A	FAS
2411	R	Sentinel physical finding(s) / no alcohol exposure
2412	L	Sentinel physical finding(s) / alcohol exposure unknown
2413	F	Sentinel physical finding(s) / alcohol exposed
2414	F	Sentinel physical finding(s) / alcohol exposed
2421	P	Sentinel physical finding(s) / neurodevelopmental disorder / no alcohol exposure
2422	J	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposure unknown
2423	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
2424	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
2431	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
2432	A	FAS
2433	A	FAS
2434	A	FAS
2441	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
2442	A	FAS
2443	A	FAS
2444	A	FAS

Code	Category	Diagnostic Name (4-Digit Codes under the umbrella of FASD in red font)
3111	R	Sentinel physical finding(s) / no alcohol exposure
3112	L	Sentinel physical finding(s) / alcohol exposure unknown
3113	F	Sentinel physical finding(s) / alcohol exposed
3114	F	Sentinel physical finding(s) / alcohol exposed
3121	P	Sentinel physical finding(s) / neurodevelopmental disorder / no alcohol exposure
3122	J	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposure unknown
3123	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
3124	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
3131	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
3132	H	Sentinel physical finding(s) / static encephalopathy / alcohol exposure unknown
3133	B	Sentinel physical finding(s) / static encephalopathy / alcohol exposed
3134	B	Sentinel physical finding(s) / static encephalopathy / alcohol exposed
3141	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
3142	H	Sentinel physical finding(s) / static encephalopathy / alcohol exposure unknown
3143	B	Sentinel physical finding(s) / static encephalopathy / alcohol exposed
3144	B	Sentinel physical finding(s) / static encephalopathy / alcohol exposed
3211	R	Sentinel physical finding(s) / no alcohol exposure
3212	L	Sentinel physical finding(s) / alcohol exposure unknown
3213	F	Sentinel physical finding(s) / alcohol exposed
3214	F	Sentinel physical finding(s) / alcohol exposed)
3221	P	Sentinel physical finding(s) / neurodevelopmental disorder / no alcohol exposure
3222	J	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposure unknown
3223	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
3224	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
3231	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
3232	H	Sentinel physical finding(s) / static encephalopathy / alcohol exposure unknown
3233	B	Sentinel physical finding(s) / static encephalopathy / alcohol exposed
3234	B	Sentinel physical finding(s) / static encephalopathy / alcohol exposed
3241	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
3242	H	Sentinel physical finding(s) / static encephalopathy / alcohol exposure unknown
3243	B	Sentinel physical finding(s) / static encephalopathy / alcohol exposed
3244	B	Sentinel physical finding(s) / static encephalopathy / alcohol exposed
3311	R	Sentinel physical finding(s) / no alcohol exposure
3312	L	Sentinel physical finding(s) / alcohol exposure unknown
3313	F	Sentinel physical finding(s) / alcohol exposed
3314	F	Sentinel physical finding(s) / alcohol exposed
3321	P	Sentinel physical finding(s) / neurodevelopmental disorder / no alcohol exposure
3322	J	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposure unknown
3323	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
3324	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
3331	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
3332	H	Sentinel physical finding(s) / static encephalopathy / alcohol exposure unknown
3333	A	FAS
3334	A	FAS

Code	Category	Diagnostic Name (4-Digit Codes under the umbrella of FASD in red font)
3341	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
3342	H	Sentinel physical finding(s) / static encephalopathy / alcohol exposure unknown
3343	A	FAS
3344	A	FAS
3411	R	Sentinel physical finding(s) / no alcohol exposure
3412	L	Sentinel physical finding(s) / alcohol exposure unknown
3413	F	Sentinel physical finding(s) / alcohol exposed
3414	F	Sentinel physical finding(s) / alcohol exposed
3421	P	Sentinel physical finding(s) / neurodevelopmental disorder / no alcohol exposure
3422	J	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposure unknown
3423	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
3424	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
3431	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
3432	A	FAS
3433	A	FAS
3434	A	FAS
3441	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
3442	A	FAS
3443	A	FAS
3444	A	FAS
4111	R	Sentinel physical finding(s) / no alcohol exposure
4112	L	Sentinel physical finding(s) / alcohol exposure unknown
4113	F	Sentinel physical finding(s) / alcohol exposed
4114	F	Sentinel physical finding(s) / alcohol exposed
4121	P	Sentinel physical finding(s) / neurodevelopmental disorder / no alcohol exposure
4122	J	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposure unknown
4123	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
4124	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
4131	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
4132	H	Sentinel physical finding(s) / static encephalopathy / alcohol exposure unknown
4133	B	Sentinel physical finding(s) / static encephalopathy / alcohol exposed
4134	B	Sentinel physical finding(s) / static encephalopathy / alcohol exposed
4141	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
4142	H	Sentinel physical finding(s) / static encephalopathy / alcohol exposure unknown
4143	B	Sentinel physical finding(s) / static encephalopathy / alcohol exposed
4144	B	Sentinel physical finding(s) / static encephalopathy / alcohol exposed
4211	R	Sentinel physical finding(s) / no alcohol exposure
4212	L	Sentinel physical finding(s) / alcohol exposure unknown
4213	F	Sentinel physical finding(s) / alcohol exposed
4214	F	Sentinel physical finding(s) / alcohol exposed
4221	P	Sentinel physical finding(s) / neurodevelopmental disorder / no alcohol exposure
4222	J	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposure unknown
4223	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
4224	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed

Code	Category	Diagnostic Name (4-Digit Codes under the umbrella of FASD in red font)
4231	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
4232	H	Sentinel physical finding(s) / static encephalopathy / alcohol exposure unknown
4233	B	Sentinel physical finding(s) / static encephalopathy / alcohol exposed
4234	B	Sentinel physical finding(s) / static encephalopathy / alcohol exposed
4241	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
4242	H	Sentinel physical finding(s) / static encephalopathy / alcohol exposure unknown
4243	B	Sentinel physical finding(s) / static encephalopathy / alcohol exposed
4244	B	Sentinel physical finding(s) / static encephalopathy / alcohol exposed
4311	R	Sentinel physical finding(s) / no alcohol exposure
4312	L	Sentinel physical finding(s) / alcohol exposure unknown
4313	F	Sentinel physical finding(s) / alcohol exposed
4314	F	Sentinel physical finding(s) / alcohol exposed
4321	P	Sentinel physical finding(s) / neurodevelopmental disorder / no alcohol exposure
4322	J	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposure unknown
4323	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
4324	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
4331	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
4332	H	Sentinel physical finding(s) / static encephalopathy / alcohol exposure unknown
4333	A	FAS
4334	A	FAS
4341	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
4342	H	Sentinel physical finding(s) / static encephalopathy / alcohol exposure unknown
4343	A	FAS
4344	A	FAS
4411	R	Sentinel physical finding(s) / no alcohol exposure
4412	L	Sentinel physical finding(s) / alcohol exposure unknown
4413	F	Sentinel physical finding(s) / alcohol exposed
4414	F	Sentinel physical finding(s) / alcohol exposed
4421	P	Sentinel physical finding(s) / neurodevelopmental disorder / no alcohol exposure
4422	J	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposure unknown
4423	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
4424	D	Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed
4431	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
4432	A	FAS
4433	A	FAS
4434	A	FAS
4441	N	Sentinel physical finding(s) / static encephalopathy / no alcohol exposure
4442	A	FAS
4443	A	FAS
4444	A	FAS

VII. Medical Summary Report & Generic Summaries for Diagnostic Categories

The FASDPN clinic generates a single comprehensive Medical Summary Report composed jointly by the interdisciplinary team.

An example of the format and content of our report is presented below for a fictitious patient. An electronic template of our Medical Summary Report is available free (contact Susan Astley Hemingway Ph.D. (astley@uw.edu)).

<Clinic Name>
Medical Summary Report Clinic Date: mm/dd/yyyy

Diagnosis	**Fetal Alcohol Syndrome**

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of significant brain damage/dysfunction that occur in individuals exposed to alcohol during gestation. On the attached pages are the specific findings in this patient's case that confirm they meet criteria for FAS.

Although this patient meets criteria for FAS, this does not mean that alcohol exposure during pregnancy is the only cause of the patient's current challenges. Other factors could also be contributing to the present issues such as the patient's genetic background, other potential exposures or problems during gestation, and various experiences since birth. Such factors may partly explain why there is so much variability in the kinds of specific challenges that patients with FAS have.

Individuals with FAS have significant brain damage/dysfunction and should be viewed as individuals with disabilities. This FAS diagnosis has implications for educational planning, societal expectations, and health. On the attached sheets you will find a list of specific concerns that have been identified that need attention.

_____
<Name>, MD
<Name of Clinic>

Medical Summary Report <Patient name & birth date> p 1 of 18

Diagnosis: Fetal Alcohol Syndrome (4-Digit Code 4433)

FASD 4-Digit Code

Rank	4 Growth	4 Face	3 Brain	3 Prenatal Alcohol	3 Other Prenatal Risks	3 Other Postnatal Risks
4	severe	all 3 features	abnormal structure/neurology	high	high	high
3	moderate	2.5 features	severe dysfunction	some	some	some
2	mild	1-2 features	moderate dysfunction	unknown	unknown	unknown
1	normal	no features	normal function	none	none	none

Overview of Evaluation Procedure:

<Name> (10.2 of age) was accompanied today (mm/dd/yyyy) in clinic by his adoptive parents. A 4-hour interdisciplinary diagnostic evaluation using the 4-Digit Diagnostic Code[1] was conducted by the Fetal Alcohol Syndrome Diagnostic & Prevention Network (FASDPN) interdisciplinary clinical team composed of a pediatrician (<Name>, MD), an occupational therapist (<Name>, PhD, OTR/L), speech/language pathologist (<Name>, PhD, CCC-SLP), psychologist (<Name>, PhD), social worker (<Name>, MSW), family advocate (<Name>) and clinic director (<Name>, PhD). In the weeks leading up to this clinic appointment, prior school, medical, psychological and social service records were obtained and reviewed by the social worker. In addition, the patient's caregivers completed standardized questionnaires. Upon arrival today, the patient had his height, weight, and OFC measured and a clinical photograph taken of his face. Concurrently, the FASDPN diagnostic team participated in a 30-minute case presentation conducted by the social worker. Upon completion of the case presentation, the team pediatrician and social worker conducted a joint clinical interview with the caregivers. Concurrently, the patient received a 2-hour multi-disciplinary screening conducted by the occupational therapist, speech/language pathologist and psychologist. The team reconvened for 75 minutes and derived a diagnosis and treatment plan. The team shared the diagnosis with the patient's parents in the final 30 minutes of the appointment. The psychologist scheduled a 30-minute telephone conference with the caregivers for the following week to discuss the intervention recommendations.

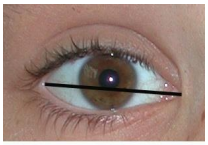
1. S.J (Astley) Hemingway. Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code. 4th Edition, Seattle WA: University of Washington Publication Services, 2024.

Growth:

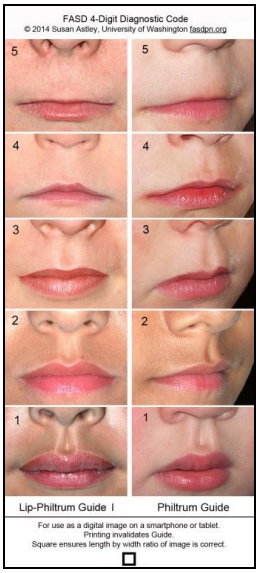
Individuals with FASD are often growth deficient either pre- or postnatally. Two key indices for growth are height and weight percentiles adjusted for age. <Patient's name> presents with severe growth deficiency (Growth ABC-Score = CC; Growth Rank 4) based on his postnatal measurements. After a birth ending in the 38th week of gestation, <Patient's name> was 44.8 cm in length (7th percentile) and weighed 2,879 g (20th percentile). His current height and weight are 130.2 cm (3rd percentile after adjustment for midparental height) and 23.7 kg (3rd percentile).

Face:

The face of fetal alcohol syndrome is characterized by the presence of all three of the following features: small eyes (as measured by palpebral fissure length), a thin upper lip and a smooth philtrum (the vertical groove between the nose and the upper lip). The palpebral fissures must be two or more standard deviations below the norm and the thin upper lip and smooth philtrum must be a Rank 4 or 5 on the Lip-Philtrum Guide. Based on the 4-Digit Code, if all three of these features are present, the Face is assigned a Rank 4. Moderate and mild expressions of these FAS facial features receive Face Ranks of 3 and 2 respectively. If none of these three facial features are present, the face receives a Rank 1.



palpebral fissure length



<Patient's name> palpebral fissure lengths were significantly small (22.4 mm, estimated to be 3.75 SDs below the mean on the Stromland PFL growth charts) for his age and race (Caucasian). <Patient's name> has a very smooth philtrum (Rank 5) and a moderately thin upper lip (Lip Circularity = 79.5; Rank 4) based on the use of UW Lip-Philtrum Guide 1. Based on these facial measures, <Patient's name> receives a Facial ABC-Score of CCC (or 4-Digit Face Rank 4). <Patient's name> presents with the full expression of the FAS facial phenotype. <Patient's name> also presented with hypertelorism (inner canthal distance 35.1 mm, estimated to be 2.01 SDs above the mean on the Hall inner canthal distance growth charts). In addition, <Patient's name> presented with epicanthal folds. See FAS Facial Photographic Analysis Software photo report below.

FAS Facial Photographic Analysis Report

IDENTIFICATION

Name: Name (First) Name (Middle) Name (Last)
Subject I.D.:
Source of Photo: Clinic Name
Gender: Male
Race: Caucasian / Caucasian
Birth Date: mm/dd/yyyy

PHOTO ASSESSMENT

Normal PFL Chart: Scandinavian (Stromland '99) Lip-Philtrum Guide: Caucasian
Normal ICD Chart: Caucasian (Hall '89)

	Frontal	¾ View	Lateral
File Name	frontal.jpg	oblique.jpg	lateral.jpg
Date of Photo	mm/dd/yyyy	mm/dd/yyyy	mm/dd/yyyy
Age (yrs) in photo	10.2	10.2	10.2
Date of Photo Assessment	mm/dd/yyyy	mm/dd/yyyy	mm/dd/yyyy
Photo Assessor	name	name	name

Length of Real Internal Measure of Scale(sticker) placed on forehead (mm): 19.05
Length of Internal Measure of Scale in Frontal Photo (pixels): 122.5

Left Palpebral Fissure Length:	In photo (pixels) 129.0	True Length (mm) 22.1	Z-score -3.97
Right Palpebral Fissure Length:	In photo (pixels) 132.5	True Length (mm) 22.7	Z-score -3.52
Mean Palpebral Fissure Length:	In photo (pixels) 130.8	True Length (mm) 22.4	Z-score -3.75
Inner Canthal Distance (ICD):	In photo (pixels) 226.0	True Distance (mm) 35.1	Z-score 2.01

Flat Philtrum (5-point rank): In Frontal Photo 5 In ¾ Photo 5
Thin Upper Lip: Circularity (perimeter²/area) 79.5 5-Point rank (Circ) 4 5-Point rank (Scale) 4

clown eyebrows ☐ ptosis ☐ strabismus ☐ epicanthal folds ■
flat midface ☐ protruding ears ☐ flat nasal bridge ☐ hypertelorism ■

Other anomalies present: None reported

Comments:
Other syndromes present: None reported

PHOTO QUALITY

	Frontal	¾ View	Lateral
Side showing		Right	Left
Head rotation (5-point rank/degrees) to subject's Right (+) or Left (-)	1°	0	0
Head tilt (5-point rank) toward subject's Right (+) or Left (-) shoulder			0
Head tip (degrees) Up (+) or Down (-) from Frankfort Horizontal Plane	1°		
Exposure (3-point rank)	1 (good)	1 (good)	1 (good)
Focus (3-point rank)	1 (good)	1 (good)	1 (good)
Facial Expression (3-point rank)	1 (Relaxed)	1 (Relaxed)	1 (Relaxed)
Reliability of ABC-Score for palpebral fissure length (5-point rank)	1 (very good)		
Reliability of ABC-Score for philtrum (5-point rank)	1 (very good)	1 (very good)	
Reliability of ABC-Score for upper lip (5-point rank)	1 (very good)		

Photo Photo Photo
Frontal.jpg oblique.jpg lateral.jpg

OUTCOME

ABC-Score: C (PFL) C (Philtrum) C (Lip)
Data Used: mean 3/4 View circularity

4-Digit Diagnostic Code for Face: 4: FAS features severe

University of Washington FAS DPN FAS Facial Photographic Analysis Software

Brain: Brain damage may be evidenced by abnormal brain structure (such as microcephaly or abnormal structure identified through brain imaging), abnormal neurological signs of presumed prenatal origin (such as seizures, tics or spasticity) and/or significant brain dysfunction as measured by standardized psychometric assessments. Based on the 4-Digit Diagnostic Code, a Brain Rank 4 is assigned when structural and/or neurological evidence of impairment is present, a Brain Rank 3 is assigned when there is evidence of significant brain dysfunction, a Brain Rank 2 is assigned when there is some evidence of brain dysfunction or delayed development, but not at the level of a Rank 3 and a Brain Rank 1 is assigned when there is no functional evidence of impairment.

Based on the information available to us to date, <Patient's name> met the criteria for a Brain Rank 3. This information is described more fully below.

Structurally, <Patient's name> head circumference has always been in the normal range. At birth his OFC was 32.7 cm (37th percentile for 38 weeks gestation) and is currently 51 cm (20th percentile). <Patient's name> has had his brain imaged. A cranial ultrasound in <year> was reported normal. Neurologically, <Patient's name> does not have a reported history of seizures or other neurologic problems.

Brain or central nervous system function was assessed both prior to and during this clinic visit.

Psychometric assessments administered today in clinic include the following:

Psychological Screen:
- *California Verbal Learning Test- Children's Version (CVLT-C)*
- *Child Behavior Checklist for Ages 6-18 (CBCL/6-18)*
- *Children's Sleep Habits Questionnaire (CSHQ)*
- *Delis-Kaplan Executive Function System (D-KEFS)*

Motor/Sensory/Developmental Screen:
- *Developmental Test of Visual Motor Integration, 6th Edition (VMI-6)*
- *Quick Neurological Screening Test-3R (QNST-3R)*
- *Short Sensory Profile (SSP)*

Language Screen:
- *Children's Communication Checklist-2 (CCC-2)*
- *Clinical Evaluation of Language Fundamentals - 4th Edition (CELF-4)*

Previous Testing:

Records from the following previous assessments were also available for our review and consideration:
- *KTEA-3, <year>*
- *ABAS-3, <year>*
- *BASC-3, <year>*
- *BOT-2, <year>*
- WISC-5, <year>

Previous records document <Patient's name> has a diagnosis of ADHD.

The standardized testing and clinical observations carried out in this FASD diagnostic clinic are conducted solely for the purposes of diagnosing alcohol-related disabilities and making related recommendations and referrals. This is not a comprehensive assessment of skills. To more completely understand <Patient's name>'s unique cognitive and behavioral profile, additional comprehensive psychological, neuropsychological, occupational therapy and speech assessments carried out by qualified professionals may be necessary.

The test outcomes presented in this report use a variety of scoring systems. Unless otherwise indicated, Standard scores are based on a scale in which the mean is 100 and the standard deviation is 15. This means that most individuals attain a Standard score between 85 and 115 (the "average" range). Scores that are 2 or more standard deviations below the mean are considered significantly below the mean. Thus, Standard scores at or below 70 are considered to be significantly below the mean. T-scores are based on a scale in which the mean is 50 and the standard deviation is 10. An average T-score falls between 40 and 60. A T-score at or below 30 is significantly below the mean. Some subtests use Scaled scores, in which the mean is 10 and the standard deviation is 3. An average Scaled score falls between 7 and 13. A Scaled score at or below 4 is significantly below the mean. Percentile ranks indicate where the individual's score falls relative to his age peers. Average scores fall between the 25th to the 75th percentile (the 50th percentile is in the middle of the average range and corresponds to a Standard score of 100). Scores below the 3rd percentile are significantly below the average range.

Psychological Screen conducted in clinic today at chronological age 10.2 years:

It was a pleasure working with <Patient's name> today. <Patient's name> was cooperative and engaged throughout the assessment. He shared his sense of humor and was talkative. <Patient's name> used emphatic gestures, established eye contact with the examiner, and engaged in reciprocal interactions. He remained at the table throughout the assessment although he fidgeted in his chair and required movement at times. He also responded impulsively and was inattentive to details on occasion. Despite these behaviors, he put forth appropriate effort and completed every task. Snack breaks and encouragement were helpful in supporting <Patient's name>'s performance. The results reported here are believed to be a valid indicator of <Patient's name>'s current functioning in the areas assessed. Therefore, these results are considered valid estimates of his thinking and reasoning ability.

The *California Verbal Learning Test - Children's Version (CVLT-C)* is a measure of multiple components of verbal learning and memory. Strategies and processes involved in learning and recalling verbal material are also assessed. On this test, <Patient's name> received the following scores:

CVLT-C		
Task	**Level of Recall**	
List A: Total Trials	T-Score	31
List A: Short Delay Free Recall	z-score	-2
List A: Short Delay Cued Recall	z-score	-1.5
List A: Long Delay Free Recall	z-score	-1.5
List A: Long Delay Cued Recall	z-score	-1.5
List B: Free Recall	z-score	-1

CVLT-C			
Learning Characteristics	*z-score*	**Recall Errors/Recognition Measures**	*z-score*
Semantic Cluster Ratio	0	Perseverations	-0.5
Serial Cluster Ratio	-0.5	Free-recall Intrusions	1
Learning Slope	-3	Cued-recall Intrusions	2
Percent Recall Consistency	-2	Discriminability	1

<Patient's name> demonstrated significant difficulty with verbal learning and memory. Rather than increasing the number of words he recalled from a list across five repeated trials, he recalled fewer than expected resulting in a *T*-score of 31, which is in the very low range compared to his same-aged peers. He also had difficulty recalling the list after a short delay with distraction and when cued to recall items within a specific category. During these memory tasks, he tended to add words that were within the categories but were not within the initial list. This performance indicates that <Patient's name> may be overwhelmed by too much information and unable to sustain attention. Additionally, he confabulates to appear and feel more competent or to please others, which may be interpreted by others as lying. Despite the difficulty of this task, <Patient's name> persisted without complaint and put forth good effort.

Delis-Kaplan Executive Function System (D-KEFS) consists of 9 independent tests designed to measure quantitative and qualitative aspects of executive functions.

The *D-KEFS Color-Word Interference Test* typically measures inhibition and cognitive flexibility. This subtest is comprised of four conditions. The first two conditions measure speed and accuracy of naming colors and reading color names written in black ink. The third condition evaluates the ability to inhibit the name-reading response to perform the less-automatic skill of naming the color of ink, while the fourth condition examines the ability to both inhibit and switch between two sets of rules. On this measure, <Patient's name> received the following scores:

D-KEFS Color-Word Interference	
Primary Measures	**Scaled Score**
Color Naming	7
Word Reading	8
Inhibition	8
Inhibition/Switching	10
Combined Naming + Reading	7
Primary Contrast Measures	**Scaled Score**
Inhibition vs. Color Naming	10
Inhibition/Switching vs. Combined Naming + Reading	11
Inhibition/Switching vs. Inhibition	12
Error Measures	**Scaled Score**
Inhibition Condition	3
Inhibition/Switching Condition	1

<Patient's name> was able to complete each of these tasks as quickly as expected for his age; however, he sacrificed accuracy for speed and made several errors. At times, he caught his errors and self-corrected, yet for several, he was unaware that he made a mistake. The number of errors significantly exceeded expectations compared to his same-aged peers indicating impulsive responding, poor cognitive flexibility, and difficulty with self-monitoring yet age-appropriate processing speed.

The *D-KEFS Trail Making Test* is a well-known drawing test that assesses planning, organization, sequencing, motor speed, and flexible thinking skills. This task is made up of five conditions. Four of the conditions are used to isolate the four skills necessary to perform the fifth task (which measures the ability to switch sets). On this measure, <Patient's name> received the following scores:

D-KEFS Trail Making	
Primary Measures	**Completion Times Scaled Score**
Visual Scanning	12
Number Sequencing	13
Letter Sequencing	3
Number-Letter Switching	3
Motor Speed	10
Combined Number + Letter Sequencing	8
Contrast Measures	**Contrast Scaled Score**
Switching vs. Visual Scanning	2
Switching vs. Number Sequencing	2
Switching vs. Letter Sequencing	0
Switching vs. Combined Number + Letter Sequencing	5
Switching vs. Motor Speed	3
Error Analysis	**Scaled Score**
All Error Types for Number-Letter Switching	3

<Patient's name> was able to scan an array of letters and numbers, sequence numbers, and connect dots on paper with a pencil as quickly as others his age. When sequencing letters, <Patient's name> needed help remembering that H came after G rather than J and he spent quite a bit of extra time searching for the letter J and incorrectly rehearsing the alphabet. Had the examiner not assisted <Patient's name> by giving him the correct letter, he would not have completed this task. Even with the help, his score is in the very low range. On the switching task, however, <Patient's name> remembered the correct order of the alphabet yet made a significant number of errors and took extra time reviewing and rehearsing the number and letter sequences. This performance is consistent with Color-Word Interference and indicates that <Patient's name> has difficulty with impulsive responding, cognitive flexibility, and self-monitoring.

The *Child Behavior Checklist for Ages 6-18 (CBCL/6-18)* is a caregiver checklist reporting on children's social competence and behavior problems. This questionnaire presents: (1) a list of behavior problems which are rated by the parent for frequency of occurrence (high scores reflect

deficits); and (2) a series of questions about social activities and school performance to provide information on the child's degree of participation in these activities and at school, and the quality of the child's performance (low scores reflect deficits). The patient's caregiver completed this checklist on mm/dd/yyyy. The caregiver's responses yielded the following scores:

CBCL/6-18			
Index/Scale	**T-Score**	**Behavior Problem Scales**	**T-Score**
Total Competence	**30-C**	Anxious/Depressed	66-B
Activities	52	Withdrawn/Depressed	68-B
Social	28-C	Somatic Complaints	72-C
School	24-C	Social Problems	70-C
Total Behavior Problems	**73-C**	Thought Problems	71-C
Internalizing	71-C	Attention Problems	92-C
Externalizing	65-C	Rule-Breaking Behavior	67-B
		Aggressive Behavior	64

B= scores are in the Borderline Range, C=scores are in the Clinical Range

The caregiver's ratings indicated that they perceive significantly elevated Externalizing and Internalizing Behaviors. The caregiver endorsed items indicating that <Patient's name> has Clinical levels of inattention, impulsivity, and social problems. Rule-breaking behaviors, such as lying, and thought problems, such as hording items and getting stuck on specific characters were reported. The caregiver also noted that <Patient's name> has a tendency to be moody and argumentative. Several ratings were consistent with <Patient's name>'s medical problems and diagnoses of attention deficit hyperactivity disorder and anxiety. Additionally, the caregiver reported concerns with school performance and academic learning in all areas. <Patient's name> currently has an Individualized Education Plan (IEP) at school. <Patient's name> was reported to get along with others and has friends. He engages in some age-appropriate activities such as soccer, basketball, and running. He also enjoys playing video games and drawing. Positively, the caregiver described <Patient's name> as loving towards friends, family, and pets. He cares greatly about people around him and is sympathetic when they are sad. He loves entertaining people and joking around.

The *Children's Sleep Habits Questionnaire (CSHQ; Owens 2000.)* Sleep disorders in children are often under-diagnosed. In children with Fetal Alcohol Spectrum Disorders, objective data on the presence of increased sleep disorders are emerging. Therefore, <Patient's name>'s caregiver was administered the CSHQ, which is a validated screening tool for identifying school-aged children with a possible sleep disorder. The CSHQ focuses on sleep disorders common to this age group in three domains: Dyssomnias, Parasomnias, and Sleep-Disordered Breathing. <Patient's name> scored 35 out of a possible 99 points. A score of 39 or higher reflects a potential sleep problem. Based on the CSHQ and parent interview, a referral to a sleep specialist is not indicated.

Motor/Sensory/Developmental Screen at chronological age 10.2 years:

The *Short Sensory Profile* measures a caregiver's report of behaviors related to sensory processing and integration abilities. The Short Sensory Profile is a standardized questionnaire of sensory processing abilities in children ages 3 to 10 years. The scores in each category are classified as Typical Performance, Probable Difference or Definite Difference. Probable or Definite Differences may suggest sensory processing and integration difficulties that are affecting behavior and daily life. On this test, <Patient's name> received the following scores:

SSP	
Test/Subtest	**Outcome**
Total Test	definite difference
Tactile Sensitivity	typical performance
Taste/Smell Sensitivity	probable difference
Movement Sensitivity	typical performance
Under-responsive/Seeks Sensation	definite difference
Auditory Filtering	definite difference
Low Energy/Weak	definite difference
Visual/Auditory Sensitivity	probable difference

Per caregiver report, it was endorsed that <Patient's name> has strengths in the areas of tactile sensitivity and movement sensitivity and challenges in the areas of taste/smell sensitivity, under-responsive/seeks sensation, auditory filtering, low energy/weak, and visual/auditory sensitivity. Results suggest that processing sensory information is challenging for <Patient's name>, and this may account for some of the behaviors that caregivers identified as concerning (e.g., difficulty staying on task, trouble listening to directions, avoidance of self-care tasks).

The *Developmental Test of Visual Motor Integration, 6th Edition (VMI-6)* measures eye-hand coordination copying various geometric forms of increasing complexity. Results on the VMI suggest that <Patient's name>'s visual motor skills are at the 2nd percentile range (standard score 70), placing his performance significantly below the average range when compared to same age peers.

VMI	
Test	Standard Score
VMI	70
Visual Perception	110
Motor Coordination	73

<Patient's name> received a standard score of 110 for visual perception (75th percentile), placing his performance in the average range. <Patient's name> received a standard score of 73 for motor coordination (4th percentile), placing his performance in the below average range. He would benefit from handwriting support and accommodations (e.g. learning to keyboard).

The *Quick Neurological Screening Test-3R (QNST-3R)* is a screening tool that measures neurological soft signs in ages 5 years of age through adulthood. It consists of items adapted from neurologic and neuropsychological examinations that sample fine and gross motor coordination, balance and vestibular function, visual and auditory perceptual skills, motor planning and sequencing, and spatial organization. Items on the QNST-3 reflect measures of neurological maturation or integrity. Deficient performance on several of these measures may be suggestive of an underlying developmental or neurological basis for learning or behavioral problems. Scores fall into one of three categories 1) Normal indicates performance at or above the 25th percentile; 2) Moderate Discrepancy indicates performance in the 6th through 25 percentile and 3) Severe Discrepancy indicates performance in the 5th percentile or lower. On this measure, <Patient's name> received an overall raw score of 58, which falls into the Severe Discrepancy category for a child his age.

<Patient's name> was cooperative and worked hard throughout the screening today. When asked to write a sentence, <Patient's name> remembered the sentence and demonstrated good spacing, but he struggled with letter sizing, line use, mixing upper- and lower-case letters, and overall legibility. <Patient's name> held the pencil in his right hand using an efficient tripod grasp. Although he has a good pencil grasp, <Patient's name> fatigued quickly during paper and pencil tasks. He would benefit from handwriting support and accommodations (e.g. learning to keyboard).

<Patient's name> was able to match shapes and skip for thirty feet, but he had difficulty with visual tracking, remembering and repeating patterns, and spatial awareness. Activities that required visual-motor integration (e.g. copying shapes), fine motor coordination (e.g. mazes), motor planning, strength/endurance, bilateral coordination, static balance (e.g. standing on one foot) and dynamic balance (e.g. walking on a line backwards) were also very challenging for him. He benefited from structure, sensory supports (e.g. a quiet room, movement breaks), and a reward system (e.g. verbal praise). <Patient's name> is a sensitive, creative, and engaging boy who was a pleasure to work with!

Language Screen at chronological age 10.2 years:

<Patient's name> came to clinic without previous speech-language testing. Results from today's assessment indicate age-appropriate language development at this time. Results are based on standardized testing, caregiver report, and structured clinical observations. Details presented below.

The *Children's Communication Checklist-2 (CCC-2)* is a parent-report checklist that assists in identifying communication problems. <Patient's name>'s caregiver completed this checklist and he received the following scores:

CCC-2			
Scale	**Scaled Score**	**Composite**	**Percentile**
Speech	5		5
Syntax	10		50
Semantics	3		1
Coherence	4		2
Initiation	7		16
Scripted Language	3		1
Context	7		16
Nonverbal Communication	6		9
Social relations	5		5
Interests	6		9
General Communication Composite	45	**74**	4
Social Interaction Difference Index (SIDI)	**2:** This score is in the expected range		

Results of this caregiver questionnaire indicate concerns for <Patient's name>'s overall success as a communicator with a General Communication Composite score of 74, where most children receive scores between 85 and 115 and lower scores indicate more concern. His pattern of performance indicates the most concern for vocabulary (semantics), coherence/organization of communication, and reliance on scripted language. Strengths include grammar (syntax), initiation, and use of context.

The *Clinical Evaluation of Language Fundamentals - 4th Edition (CELF-4)* examines an individual's grasp of the relationships among semantics, syntax/morphology, and pragmatics (form, content, and use) and the interrelated domains of receptive and expressive language. On this test, <Patient's name> received the following scores:

CELF-4	
Scaled Scores: scores between 7 and 13 are expected	
Formulated Sentences	12
Word Classes-Total	9
Word Classes-Receptive	9
Word Classes-Expressive	9

Results indicate age-appropriate development of grammar and vocabulary at this time.

Structured observations during today's assessment indicated that <Patient's name> uses an age-appropriate range of vocabulary in grammatical sentences to meet an expected range of communicative functions. He engages in reciprocal conversations, responds to and asks questions, shares personal experiences and opinions, clarifies messages, requests, uses humor, comments, explains, and uses language to problem solve. He provides his listener with background information to support understanding, organizes his information appropriately, and uses idioms appropriately to sustain engagement and convey his attitude/opinion.

Taken together these results indicate that language and discourse skills are a strength that <Patient's name> can use to support his access to strategies supporting other areas that may be more challenging for him.

Despite age-appropriate language development at this time, <Patient's name>'s prenatal alcohol exposure and early medical history are a risk for difficulty with later-developing, more complex aspects of language. Progress in this and all academic areas should be closely monitored so that appropriate support can be put in place.

Summary of Psychometric Assessments of Brain Function:

<Patient's name> came to clinic today with previous neurodevelopmental testing indicating moderate concerns for written expression, mathematics, adaptive skills, and motor development. There are moderate concerns for behavior, social skills, sleep, and adaptive skills. There are previous diagnoses including attention-deficit/hyperactivity disorder and attachment disorder. He has an individualized education program supporting academics, adaptive skills, and behavior.

Today's assessment indicated significant impairment (i.e., performance two or more standard deviations below the mean on standardized testing) in sensory-motor development (e.g., visual-motor integration, visual tracking, spatial awareness, motor planning, static and dynamic balance), in verbal memory/learning, executive functioning (performance monitoring, cognitive flexibility, inhibition). Definite differences in sensory processing were documented (sensory seeking, low-energy week, auditory attention).

Caregiver Interview:

We had the pleasure of interviews with <Patient's name>'s caregivers. His caregivers expressed concerns about <Patient's name>'s growth deficiency and noted that he is very smart but inattentive. He is eating better, sleeping well, and socially successful. Parents report <Patient's name> does well with lists and routines but struggles with multistep instructions. <Patient's name> is inattentive and can be quite impulsive, especially in answering questions before the question is finished and figuring out if he knows the answer. He rapidly cycles through activities but gets bored easily. It takes <Patient's name> longer to learn new academic skills and games, and he has inconsistent retrieval of learned information. He frequently has word recall and word mix-up challenges. Socially, <Patient's name> is very social and makes friends easily from age 5 to 15; he does misinterpret social scenarios at times. His motor abilities have been impacted by lower stamina, strength, and speed. <Patient's name> has so many strengths, including his inventive game characters, having excellent humor, and being social and kind.

Alcohol Exposure:
<Patient's name>'s biological mother confirmed she drank alcohol during this pregnancy, although the exact quantities, frequency, and timing of alcohol use during pregnancy were not reported. Confirmed exposure, but of unknown quantity or frequency, meets the 4-Digit Diagnostic criteria for an Alcohol Rank 3.

Co-Morbidities
When assessing the potential impact of prenatal alcohol exposure on an individual, it is important to document all other significant prenatal and postnatal exposures and events, for they too serve as potential risk factors for cognitive/behavioral dysfunction. Prenatal risk factors may include, but are not limited to poor prenatal care, genetic conditions that may run in the family and other potential teratogenic exposures. Postnatal risk factors may include but are not limited to perinatal difficulties, adverse home environments, multiple home placements, neglect, abuse and other events that could explain brain dysfunction like head injuries or a patient's own chronic substance abuse. While it is not possible with today's medical technology to determine which risk factor(s) may be responsible for each adverse outcome, it remains important to document all exposures and events and take them into consideration when deriving a diagnosis and intervention plan.

Potential risk factors reported to the clinic to date include:

Prenatal Rank 3:
- No prenatal care.
- Tobacco use during pregnancy

Postnatal Rank 3:
- Some neglect birth to 3 years of age.
- One out of home placement at 3 years of age.

The next section of the Medical Summary Report is the Intervention Recommendations. The intervention section starts on a new page so it can be shared with schools while maintaining the medical confidentiality of the information in the first section of the report. These recommendations cover a wide range of needs: medical, education, mental health, family support, community-based programs and activities, and anticipatory guidance (Jirikowic et al., 2010). The intervention recommendations below are reflective of what is generally available in Washington State in the 2020s. Availability of services will vary considerably by community and region worldwide.

Diagnosis: Fetal Alcohol Syndrome

Intervention Recommendations

Based on records review and assessments, observations and caregiver interviews completed today by the FASDPN interdisciplinary team, the following recommendations are offered:

A. Medical

Please note that recommendations that involve medical issues should be shared with <Patient's name>'s primary care physician before initiating any action.

A. <Patient's name> has been receiving excellent general and specialty medical care. Continue regular medical & dental checkups, specialty follow up, and periodic hearing/vision screenings.

B. <Patient's name> has unusually short palpebral fissure lengths (eye openings). If not already performed, he would benefit from a comprehensive ophthalmology evaluation that includes visualization of retina and optic nerve, as we might expect associated ophthalmological findings such as refractive errors, strabismus and fundus abnormalities.

C. <Patient's name>'s ADHD is having an impact on his performance. It could be worth another trial of ADHD medication. Stimulant medications could impact his growth but might be cautiously used, or you could try non-stimulant long-acting alpha-agonists.

B. Education

- <Patient's name> will continue to benefit from an individualized education program (IEP) to support his challenges with learning as a student with other health impairment. He will continue to benefit from support in adaptive, behavior, mathematics, reading, and written language skills. We would recommend that an occupational therapist be a part of his team to support fine motor skills (handwriting) and sensory processing needs. <Patient's name>'s impairments in sensory-motor development represent an important barrier to his access to age-appropriate curriculum and educational activities.

    - Sensory accommodations are recommended. Examples are a "wiggle pad" or a weighted lap pillow to be used during the school day or in homework sessions.
    - Modifications of the classroom environment may be useful, such as a "quiet office" space to assist in focusing at school, headphones, or the use of techniques such as keyboarding. Recess is an important chance for movement, which should *never* be eliminated as a classroom discipline strategy or to complete assignments. Scheduled "down time" in a quieter, calmer space can help. The occupational therapist (OT) at school or in a private practice should be able to consult on environmental modifications and sensory accommodations.
    - A good resource for educators is the book: *Building Sensory Friendly Classrooms* by Rebecca Moyes

- If not already in place, we also recommend that the accommodations from which <Patient's name> benefits be formalized in a written plan (so that accommodations will be available now and in future educational and workplace settings). Accommodations that are important for <Patient's name> include:
  - Preferential seating and a safe place to retreat when <Patient's name> needs to self-regulate.
  - Allow extra time for testing (up to 1.5X extra) and extra time on math and writing assignments.
  - Allow testing to occur in smaller settings with reduced distractions.
  - Reduce volume of workload so that <Patient's name> does not have to work longer than peers and thus miss opportunities for other extracurricular opportunities.
  - Allow extra time for processing (for example, when answering a question in class, wait longer for <Patient's name> to formulate an answer).
  - Have instructions presented in visual form (written) rather than just verbally stated.
  - After a period of learning/ instruction, provide a break so that <Patient's name> can be ready for new learning.
  - Identify a "trusted-adult" mentor that <Patient's name> can go to for help managing stress/anxiety.
  - Time-ins (with the teacher or trusted adult) versus time-out.

- Additional resources for children with prenatal alcohol exposure:
  - *Teaching Students with Fetal Alcohol Spectrum Disorder* https://depts.washington.edu/fasdpn/pdfs/teaching-students-with-fasd-2004.pdf
  - *Fetal Alcohol Spectrum Disorders Education Strategies* https://depts.washington.edu/fasdpn/pdfs/FASD%20Educational%20Strategies%20Handbook.pdf

C. Mental Health

- Continued counseling to support the development of emotion/behavior regulation and coping strategies is recommended. Cognitive Behavioral Therapy (CBT) is an evidence-based therapeutic intervention that has been shown to be an effective therapeutic modality with many individuals <Patient's name>'s age. Additionally, there is scientific data to support "mindfulness approaches" to emotion regulation, stress management, and improving life function. There are books that can teach people how to use mindfulness in daily life, such as *The Mindfulness Solution: Everyday Practices for Everyday Problems*, by Ronald Siegel and *The Yes Brain: How to Cultivate Courage, Curiosity, and Resilience in Your Child*, by Daniel Siegel and Tina Bryson.

  - <Patient's name> has experienced intrusive comments about his medical issues from peers. One aspect of therapy that would be helpful is role-playing responses to such comments and questions.
  - Continue to closely monitor <Patient's name>'s mental health as he develops so that appropriate support can be put in place if the need arises.

D. Family Support

- Here are several parenting resources for FASD:
  - FASD Parenting Toolkit (https://adai.uw.edu/fasdtoolkit/parents.htm) is available from the University of Washington
  - The CDC has a number of FASD resources – https://www.cdc.gov/ncbddd/fasd/families.html
  - Making Sense of Fetal Alcohol Spectrum Disorder (FASD) –
  - https://www.nhsaaa.net/media/5702/fasd-info-for-parents-carers-online.pdf is an excellent resource
  - Proof Alliance (https://www.proofalliance.org) has a nice 3-page handout on Parenting Children with FASD – https://adoptmed.org/s/Parenting-children-with-FASD.pdf
  - FASD United (https://fasdunited.org/index.php/tools-for-parents-and-caregivers/) has many tools and resources for parents
  - We also like Parenting Children with Affected by FAS: A Guide for Daily Living – https://adoptmed.org/s/daily_guide_for_living.pdf

- Because of the high maintenance and complexity of raising children who are prenatally exposed to alcohol, a resource such as The National Organization on Fetal Alcohol Syndrome Washington State (NOFAS Washington) is recommended. They provide programs such as FASt Friends (a caregiver and community provider support network), family summer camps, social skills and friendship groups, and online support. www.nofaswa.org..

E. Community-based Programs and Activities

- Continue to seek opportunities to participate in extracurricular activities in supervised and structured settings. This can provide positive social experiences, mentorship, and enjoyable and successful free time activities. Possibilities include therapeutic horseback riding, Boys and Girls Club, martial arts, Outdoors-for-All, swimming lessons, choir, gymnastics, and dance.
  - Information can be obtained at https://outdoorsforall.org

- A blended Special Olympics program (http://specialolympicswashington.org) could be a lovely way to work on <Patient's name>'s physical skills and help regulate his emotions.

- Martial arts provide many benefits that can include improvements in sensory-motor, emotional self-regulation, peer interaction, and self-confidence. Kung Fu Northwest is one local option. https://www.marysvillemartialarts.com/

- Consider involvement in music and theater activities. These activities could provide <Patient's name> with social connections and be an avenue for him to explore vocational and recreational interests that can continue throughout his life.

F. Anticipatory Guidance

- <Patient's name>'s genetic history and prenatal exposures place him at high risk for developing challenges with drug and alcohol abuse and dependence. We recommend that developmentally appropriate prevention education begin very early and be repeated regularly and often. This type of education is important for children, and will remain important through elementary, middle school, and high school. The social lessons learned about alcohol at home are an important component of this education process.

- We strongly encourage all caregivers to pursue avenues of self-care, including respite care opportunities, to ensure they may continue parenting as effectively as possible.

It was a pleasure seeing <Patient's name> in clinic today.
If you have any questions, please call our clinic <phone number>.

_____

<Name>, MD
<Name of Clinic>

Generic First Page of Medical Summary Report

Note the first page of the Medical Summary Report above has a generic description of the diagnosis. The generic descriptions of all 19 Diagnostic Categories (A-S) are presented below. Simply copy and paste the generic description below that matches the patient's diagnosis into page 1 of the patient's Medical Summary Report. The text may require minor alterations or additions to conform to the specifics of an individual case. Diagnoses in red font are broadly under the umbrella of FASD.

A.
Diagnosis: Fetal Alcohol Syndrome

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of significant brain damage/dysfunction that occur in individuals exposed to alcohol during gestation. On the attached pages are the specific findings in this patient's case that confirm they meet criteria for FAS.

Although this patient meets criteria for FAS, this does not mean that alcohol exposure during pregnancy is the only cause of the patient's current challenges. Other factors could be contributing to the present issues such as the patient's genetic background, other potential exposures or problems during gestation, and various experiences since birth. Such factors may partly explain why there is so much variability in the kinds of specific challenges that patients with FAS have.

Individuals with FAS have significant brain damage/dysfunction and should be viewed as individuals with disabilities. This FAS diagnosis has implications for educational planning, societal expectations, and health. On the attached sheets you will find a list of specific concerns that have been identified that need attention.

B.
Diagnosis: Sentinel physical finding(s) / static encephalopathy / alcohol exposed

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of brain damage/dysfunction in individuals exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, some but not all the characteristic growth and facial features associated with FAS were present and there was evidence of significant brain damage and/or dysfunction as you will see noted on the attached pages. There was also a confirmed history of exposure to alcohol during gestation. These outcomes meet the criteria for *Sentinel physical finding(s) / static encephalopathy / alcohol exposed*. The patient's brain abnormalities may include structural, neurological and/or functional problems. The diagnosis of *Sentinel physical finding(s) / static encephalopathy* in the presence of alcohol exposure does not mean that alcohol is the only cause of the problem. Other factors could be contributing to the present issues such as the patient's genetic background, other potential exposures or problems during gestation, and various experiences since birth. These kinds of differences may partly explain why there is so much variability in the kinds of specific challenges that patients with static encephalopathy and alcohol exposure have.

Individuals with *Static encephalopathy* have significant brain damage/dysfunction and should be viewed as individuals with disabilities. The diagnosis of *Static encephalopathy* has implications for educational planning, societal expectations, and health. On the attached sheets you will find a list of specific problems that have been identified that need attention.

C.
Diagnosis: Static encephalopathy / alcohol exposed

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of brain damage/dysfunction occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, no growth deficiency or characteristic set of facial features were found, but there was evidence of significant brain damage/dysfunction as you will see noted on the attached pages. There was also a confirmed history of exposure to alcohol during gestation. These outcomes meet the criteria for S*tatic encephalopathy / alcohol exposed*. The patient's brain abnormalities may include structural, neurological and/or functional problems. The diagnosis of *Static encephalopathy* in the presence of prenatal alcohol exposure does not mean that alcohol is the only cause of the problem. Other factors could be contributing to the present issues such as the patient's genetic background, other potential exposures or problems during gestation, and various experiences since birth. These kinds of differences may partly explain why there is so much variability in the kinds of specific challenges that patients with static encephalopathy and alcohol exposure have.

Individuals with *Static encephalopathy* have significant brain damage/dysfunction and should be viewed as individuals with disabilities. The diagnosis of S*tatic encephalopathy* has implications for educational planning, societal expectations, and health. On the attached sheets you will find a list of specific problems that have been identified that need attention.

D.
Diagnosis: Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of significant brain damage/dysfunction occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, some or all the characteristic growth and facial features associated with FAS were present and there was evidence of brain dysfunction as you will see noted on the attached pages. There was also a confirmed history of exposure to alcohol during gestation. These outcomes meet the criteria for *Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposed*. The diagnosis of *Sentinel physical finding(s) / neurodevelopmental disorder* in the presence of alcohol exposure does not mean that alcohol is the only cause of the problem. Other factors could be contributing to the present issues such as the patient's genetic background, other potential exposures or problems during gestation, and various experiences since birth. These kinds

of differences may partly explain why there is so much variability in the kinds of specific challenges that patients with neurodevelopmental disorder and alcohol exposure have.

<Include the following paragraph if the patient is under 8 years of age at the time of diagnosis.>

The patient is still quite young and remains at risk for additional learning and developmental challenges because of prenatal alcohol exposure. It is important to note that the majority of children who have cognitive or other developmental challenges caused by prenatal alcohol exposure do not exhibit these challenges fully until school-age. All those working with and caring for the patient are advised to keep monitoring closely. This team would very much like to see the patient in clinic again to update assessment of brain functioning and overall diagnosis when the patient is old enough to allow for a broader range and depth of assessment. We invite the patient to return to our clinic after their 9th birthday. In the meantime, development should be closely monitored.

Individuals with *Neurodevelopmental Disorder* have brain damage/dysfunction and should be viewed as individuals with disabilities. This diagnosis of *Neurodevelopmental disorder* has implications for educational planning, societal expectations, and health. On the attached sheets you will find a list of specific problems that have been identified that need attention.

E.
Diagnosis: Neurodevelopmental disorder / alcohol exposed

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of significant brain damage/dysfunction in individuals exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, no growth deficiency or characteristic set of facial features were found, but there was evidence of brain dysfunction as you will see noted on the attached pages. There was also a confirmed history of exposure to alcohol during gestation. These outcomes meet the criteria for *Neurodevelopmental disorder / alcohol exposed*. The diagnosis of *Neurodevelopmental disorder* in the presence of prenatal alcohol exposure does not mean that alcohol is the only cause of the problem. Other factors could be contributing to the present issues such as the patient's genetic background, other potential exposures or problems during gestation, and various experiences since birth. These kinds of differences may partly explain why there is so much variability in the kinds of specific challenges that patients with neurodevelopmental disorder and alcohol exposure have.

<Include the following paragraph if the patient is under 8 years of age at the time of diagnosis.>

The patients is still quite young and remains at risk for additional learning and developmental challenges because of prenatal alcohol exposure. It is important to note that the majority of children who have cognitive or other developmental challenges caused by prenatal alcohol exposure do not exhibit these challenges fully until school-age. All those working with and caring for the patient are advised to keep monitoring closely. This team would very much like to see the patient in clinic again to update assessment of brain functioning and overall diagnosis when the patient is old enough to allow for a broader range and depth of assessment. We invite the patient to return to our clinic after their 9th birthday. In the meantime, development should be closely monitored.

Individuals with *Neurodevelopmental Disorder* have brain damage/dysfunction and should be viewed as individuals with disabilities. This diagnosis of *Neurodevelopmental disorder* has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

F.
Diagnosis: Sentinel physical finding(s) / alcohol exposed

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of significant brain damage/dysfunction occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

Some individuals present with growth deficiency and/or the characteristic facial features, but do not have evidence of brain damage or dysfunction. We refer to this condition as *Sentinel physical finding(s) / Alcohol exposed.* We do not consider this diagnosis under the umbrella of FASD. On the attached sheets are the specific findings in this patient's case.

<Include the following paragraph if the patient is under 8 years of age at the time of diagnosis.>

The patient is still quite young and remains at risk for additional learning and developmental challenges because of prenatal alcohol exposure. It is important to note that the majority of children who have cognitive or other developmental challenges caused by prenatal alcohol exposure do not exhibit these challenges fully until school-age. All those working with and caring for the patient are advised to keep monitoring closely. This team would very much like to see the patient in clinic again to update assessment of brain functioning and overall diagnosis when the patient is old enough to allow for a broader range and depth of assessment. We invite the patient to return to our clinic after their 9th birthday. In the meantime, development should be closely monitored.

G.
Diagnosis No sentinel physical findings or brain abnormalities detected / alcohol exposed

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of significant brain damage/dysfunction occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, we conclude they were exposed to alcohol during gestation, but no physical findings or brain abnormalities were detected at this time, as you will see noted on the attached pages. No alcohol-related diagnoses are offered at this time.

<Include the following paragraph if the patient is under 8 years of age at the time of diagnosis.>

The patient is still quite young and remains at risk for additional learning and developmental challenges because of prenatal alcohol exposure. It is important to note that the majority of children who have cognitive or other developmental challenges caused by prenatal alcohol exposure do not exhibit these challenges fully until school-age. All those working with and caring for the patient are advised to keep

monitoring closely. This team would very much like to see the patient in clinic again to update assessment of brain functioning and overall diagnosis when the patient is old enough to allow for a broader range and depth of assessment. We invite the patient to return to our clinic after their 9th birthday. In the meantime, development should be closely monitored.

H.
Diagnosis Sentinel physical finding(s) / static encephalopathy / alcohol exposure unknown

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of significant brain damage/dysfunction in individuals exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, some but not all of the characteristic growth and/or facial features associated with FAS were present, and there was evidence of significant brain damage/dysfunction as you will see noted on the attached pages. In this situation, we use the term *Sentinel physical finding(s) /Static encephalopathy/ alcohol exposure unknown* to describe the patient's condition. Although it is unknown whether this patient was exposed to alcohol during gestation, other factors could also be contributing to the patient's current cognitive/behavioral problems such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. These kinds of differences may partly explain why there is so much variability in the kinds of specific difficulties that patients with brain abnormalities have.

The diagnosis made today is based on the information available at the time of this assessment. In the event a confirmed history of alcohol exposure is obtained, then a re-evaluation would be appropriate. Alternately other birth defect syndromes or conditions not related to alcohol exposure may also need reconsideration.

Individuals with *static encephalopathy* have evidence of significant brain damage/dysfunction and should be viewed as a person with a disability. The diagnosis of *static encephalopathy* has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

I.
Diagnosis: Static encephalopathy / alcohol exposure unknown

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of significant brain damage/dysfunction occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, no growth deficiency or characteristic set of facial features were found, but there was evidence of significant brain damage/dysfunction as you will see noted on the attached pages. In this situation, we use the term *Static encephalopathy / alcohol exposure unknown* to describe the patient's condition. Although it is unknown whether this patient was exposed to alcohol during gestation, other factors could be contributing to the patient's current cognitive/behavioral problems such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth.

The diagnosis made today is based on the information available at the time of this assessment. In the event a confirmed history of alcohol exposure is obtained then a re-evaluation would be appropriate. Alternately other birth defect syndromes or conditions not related to alcohol exposure may also need reconsideration.

Individuals with *Static encephalopathy* have evidence of significant brain damage/dysfunction and should be viewed as individuals with disabilities. The diagnosis of *Static encephalopathy* has implications for educational planning, societal expectations, and health. On the attached pages you will find a list of specific problems that have been identified that need attention.

J.

Diagnosis: Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposure unknown

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of significant brain damage/dysfunction occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, some or all the characteristic growth and facial features associated with FAS were present and there was evidence of brain dysfunction as you will see noted on the attached pages. These outcomes meet the criteria for *Sentinel physical finding(s) / neurodevelopmental disorder / alcohol exposure unknown*. Although it is unknown whether this patient was exposed to alcohol during gestation, other factors could be contributing to the patient's current cognitive/behavioral problems such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth.

The diagnosis made today is based on the information available at the time of this assessment. In the event a confirmed history of alcohol exposure is obtained then a re-evaluation would be appropriate. Alternately other birth defect syndromes or conditions not related to alcohol exposure may also need reconsideration.

Individuals with *Neurodevelopmental disorder* have evidence of brain dysfunction and should be viewed as individuals with disabilities. The diagnosis of *Neurodevelopmental disorder* has implications for educational planning, societal expectations, and health. On the attached pages you will find a list of specific problems that have been identified that need attention.

K.

Diagnosis: Neurodevelopmental disorder / alcohol exposure unknown

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of significant brain damage/dysfunction in individuals exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, none of the characteristic growth and facial features associated with FAS were present and there was evidence of brain dysfunction as you will see noted on the attached pages. These outcomes meet the criteria for Neurodevelopmental *disorder / alcohol exposure*

unknown. Although it is unknown whether this patient was exposed to alcohol during gestation, other factors could be contributing to the patient's current cognitive/behavioral problems such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth.

The diagnosis made today is based on the information available at the time of this assessment. In the event a confirmed history of alcohol exposure is obtained a re-evaluation would be appropriate. Alternately other birth defect syndromes or conditions not related to alcohol exposure may also need reconsideration.

Individuals with *neurodevelopmental disorder* have evidence of brain dysfunction and should be viewed as individuals with disabilities. This diagnosis of *neurodevelopmental disorder* has implications for educational planning, societal expectations, and health. On the attached sheets you will find a list of specific problems that have been identified that need attention.

L.
Diagnosis: Sentinel physical finding(s) / alcohol exposure unknown

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of significant brain damage/dysfunction occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, some or all the characteristic growth and facial features associated with FAS were present but there was no evidence of brain abnormalities as noted on the attached pages. These outcomes meet the criteria for *Sentinel physical finding(s) / alcohol exposure unknown*. Although it is unknown whether this patient was exposed to alcohol during gestation, other factors could be contributing to the patient's current cognitive/behavioral problems such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth.

The diagnosis made today is based on the information available at the time of this assessment. In the event a confirmed history of alcohol exposure is obtained, a re-evaluation would be appropriate. Alternately other birth defect syndromes or conditions not related to alcohol exposure may need consideration.

M.
Diagnosis: No sentinel physical finding(s) or brain abnormalities detected / alcohol exposure unknown

In this current assessment, it is unknown whether or not this patient was exposed to alcohol during gestation. Furthermore, no characteristic physical findings or brain abnormalities were detected in our examination.

No alcohol-related diagnoses are offered at this time. In the event a confirmed history of alcohol exposure is obtained, a re-evaluation would be appropriate.

N.
Diagnosis Sentinel physical finding(s) / static encephalopathy / no alcohol exposure

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of brain damage/dysfunction in individuals exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, some but not all the characteristic growth and facial features associated with FAS were present and there was evidence of significant brain damage and/or dysfunction as you will see noted on the attached pages. Since prenatal alcohol exposure was confirmed absent, the full spectrum of FASD is ruled out. These outcomes meet the criteria for *Sentinel physical finding(s) / static encephalopathy / no alcohol exposure*. The diagnosis of *Sentinel physical finding(s) / static encephalopathy* in the confirmed absence of prenatal alcohol exposure suggests other factors could be contributing to the present issues such as the patient's genetic background, other potential exposures or problems during gestation, and various experiences since birth. The physical findings may suggest that other syndrome diagnoses be considered.

Individuals with *static encephalopathy* have significant brain damage/dysfunction and should be viewed as individuals with disabilities. The diagnosis of *static encephalopathy* has implications for educational planning, societal expectations, and health. On the attached sheets you will find a list of specific problems that have been identified that need attention.

O.
Diagnosis: Static encephalopathy / no alcohol exposure

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of significant brain damage/dysfunction occurring in patients exposed to alcohol during gestation.

In this patient's case, some but not all the characteristic growth and facial features associated with FAS were present and there was evidence of significant brain damage and/or dysfunction as noted on the attached pages. Since prenatal alcohol exposure was confirmed absent, the full spectrum of FASD is ruled out. The outcomes observed in this patient meet the criteria for *Static encephalopathy / no alcohol exposure*. The diagnosis of *Static encephalopathy* in the confirmed absence of prenatal alcohol exposure suggests other factors could be contributing to the present issues such as the patient's genetic background, other potential exposures or problems during gestation, and various experiences since birth.

Individuals with *Static encephalopathy* have significant brain damage/dysfunction and should be viewed as individuals with disabilities. The diagnosis of *Static encephalopathy* has implications for educational planning, societal expectations, and health. On the attached sheets you will find a list of specific problems that have been identified that need attention.

P.
Diagnosis Sentinel physical finding(s) / neurodevelopmental disorder / no alcohol exposure

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of brain damage/dysfunction in individuals exposed to alcohol during gestation.

As noted on the attached pages, some but not all the characteristic growth and facial features associated with FAS were present and there was evidence of brain damage/dysfunction. A confirmed absence of prenatal alcohol exposure, however, rules out FASD. These outcomes meet the criteria for *Sentinel physical finding(s) / neurodevelopmental disorder / no alcohol exposure*. A confirmed absence of prenatal alcohol exposure suggests other factors could be contributing to the patient's current cognitive/behavioral problems such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. The observed physical findings may suggest that other syndrome diagnoses be considered.

Individuals with *Neurodevelopmental disorder* have evidence of brain dysfunction and should be viewed as a person with a disability. The diagnosis of *Neurodevelopmental disorder* has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

Q.
Diagnosis: Neurodevelopmental disorder / no alcohol exposure

Fetal alcohol syndrome (FAS) is defined by evidence of growth deficiency, a specific set of facial characteristics, and evidence of significant brain damage/dysfunction in individuals exposed to alcohol during gestation.

As noted on the attached pages, some but not all of the characteristic growth and facial features associated with FAS were present and there was evidence of brain damage/dysfunction. A confirmed absence of prenatal alcohol exposure, however, rules out FASD. These outcomes meet the criteria for *Neurodevelopmental disorder / no alcohol exposure*. A confirmed absence of prenatal alcohol exposure suggests other factors could be contributing to the patient's current cognitive/behavioral problems such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth.

Individuals with *Neurodevelopmental disorder* have evidence of brain dysfunction and should be viewed as a person with a disability. The diagnosis of *Neurodevelopmental disorder* has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

R.
Diagnosis: Sentinel physical finding(s) / no alcohol exposure

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of minor facial anomalies, and evidence of significant brain damage/dysfunction occurring in patients exposed to alcohol during gestation.

In this patient's case, some or all the characteristic growth and facial features associated with FAS were present but there was no evidence of brain abnormalities as noted on the attached pages. A confirmed absence of prenatal alcohol exposure rules out FASD. The outcomes observed in this patient meet the criteria for *Sentinel physical finding(s) / no alcohol exposure*. The physical findings might suggest that other syndrome diagnoses be considered.

S.
Diagnosis No physical findings or brain abnormalities detected / no alcohol exposure

In this current assessment, we conclude that this patient was not exposed to alcohol during gestation. Furthermore, no specific cognitive, behavioral, or characteristic physical findings were detected in our examination. The full spectrum of FASD is ruled-out. No diagnoses are offered at this time.

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IX. Appendices

1. FASDPN WEBSITE https://depts.washington.edu/fasdpn/index.htm

The University of Washington FASDPN website provides a comprehensive overview of all clinical, research, and training activities conducted by the FASDPN. Below are links to FASDPN publications, and 4-Digit Code training opportunities, diagnostic forms, Lip-Philtrum Guides and the FAS Facial Photographic Analysis Software. All resources listed below are available free of charge.

A. Publications

Literature published by the FASDPN since 1993.

B. 4-Digit Code TRAINING PROGRAMS AND ONLINE COURSE

i. One-Day Clinical Observational Training Program. This training provides healthcare, social service, and educational professionals with insight into their role in the community for screening, referral, diagnosis, prevention, and intervention of FASD.

ii. Two-Day Interdisciplinary Clinical Training Program. This training program is offered twice a year at the University of Washington. Interdisciplinary clinical teams are taught how to use the 4-Digit Diagnostic Code in an interdisciplinary clinical setting.

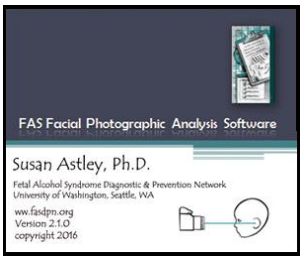
iii. FASD 4-Digit Code Online Course. This accredited course will provide healthcare, educational, and social service professionals with detailed instruction on the use of the 4-Digit Diagnostic Code in an interdisciplinary clinical setting.

A. Diagnostic Forms and Medical Summary Templates.

Electronic versions of the 4-Digit Code Diagnostic Forms are available free on the FASDPN website. An electronic template of our Medical Summary Report (see section VII) is available free (contact Susan Astley Hemingway Ph.D (astley@uw.edu)).

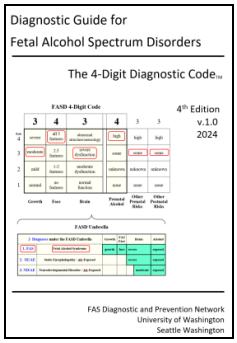
C. DIAGNOSTIC TOOLS AND SOFTWARE

i. FAS Facial Photographic Analysis Software (2016). This software is intended for use by healthcare and research professionals. The software allows one to measure the magnitude of expression of the key facial features of FAS from a 2D digital facial photograph. Video demonstration of the software. A free copy of the software can be obtained by submitting the FASDPN order form.



iii. FASD 4-Digit Diagnostic Guide (2024) and Lip-Philtrum Guides. Free electronic copies of the "*Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code, 2024*" and the *Lip-Philtrum Guides* can be ordered from the FASDPN.



2. NEW PATIENT INFORMATION FORM (NPIF) (See form below).

This form is sent to families requesting a diagnostic evaluation at the University of Washington FASDPN clinic. The form allows the family to share with the clinic why they are seeking a diagnostic evaluation, what they hope to gain from the evaluation and what they currently know about the patient's exposure(s) and outcomes. We do not expect the family to be able to respond to all requests for information on the Form. During the intake, the clinical team will also obtain and review (with caregiver consent) all medical, school, and social service records on the patient, in preparation for the evaluation. This New Patient Information form serves as a clinical intake form. Families can download the NPIF from the FASDPN website along with instructions for how to request a FASD diagnostic evaluation. At the Seattle FASDPN clinic, a confirmed prenatal alcohol exposure is the only information required to be evaluated in the clinic. The NPIF is available in electronic fillable form on our website.

New Patient Information Form FASD Clinic

Office Use: Date received ___/___/___ Deadline ___/___/___ ASAP ____ Response Let. ___/___/___ Photo ___ Screen Code _____
G _____ F _____ B _____ A _____ M _____: 1 2 3 4

Patient Identification

Patient's sex at birth _____ Gender identity _____ Race(s) _____

Patient's Name _____ Birth date _____ Age _____
First Middle Last

Patient's Address _____

City _____ County _____ State _____ zip code _____

Patient's Telephone Home ( ) _____ Work ( ) _____

Caretaker Identification

Name of patient's primary caretaker(s) _____

Relationship to patient: ❑ birth, ❑ adoptive, or ❑ foster parent ❑ other (specify _____)

Caretaker's Address

City _____ County _____ State _____ zip code _____

Telephone Home ( ) _____ Work ( ) _____

Name of patient's legal guardian(s) _____

Person Completing the Form

Name of person completing this form _____ Date _____

Relationship to patient: ❑ birth, ❑ adoptive, or ❑ foster parent, ❑ caseworker, ❑ medical care provider

❑ other relationship (specify _____)

Referred by (e.g., who or what organization told you about the clinic?) _____

Who Should Correspondence be Sent To?

Name _____

Relationship to patient: ❑ birth, ❑ adoptive, or ❑ foster parent ❑ other (specify _____)

Address _____

City _____ County _____ State _____ zip code _____

Telephone Home ( ) _____ Work ( ) _____

Please complete this form to the best of your ability. We realize you will not have the answers to all questions. All information requested in this form is important in allowing us to provide you with the most accurate diagnosis and most appropriate referrals for care. Thank you for taking the time to complete it.

Reasons for Evaluation What are the patient's primary problems? Please be specific.

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

What do you hope to gain from the evaluation?

_____

_____

_____

_____

_____

_____

_____

Growth

Birth Measures

1. Birth weight: lbs / oz _____ or gms _____

   Birth length: inches _____ or cm _____

   Birth head circumference: inches _____ or cm _____

   Gestational age *(length of pregnancy)*: weeks _____ or months _____

Please provide additional height, weight and head measures if available*

2. Date _____ Weight: lbs _____ or kg _____

   Age _____ Height: inches _____ or cm _____

   Head Circumference: inches _____ or cm _____

3. Date _____ Weight: lbs _____ or kg _____

   Age _____ Height: inches _____ or cm _____

   Head Circumference: inches _____ or cm _____

4. Date _____ Weight: lbs _____ or kg _____

   Age _____ Height: inches _____ or cm _____

   Head Circumference: inches _____ or cm _____

5. Date _____ Weight: lbs _____ or kg _____

   Age _____ Height: inches _____ or cm _____

   Head Circumference: inches _____ or cm _____

Birth Parents' Heights: Birth Mother: inches _____ or cm _____

Birth Father: inches _____ or cm _____

* This information may be available from the patient's physician or school nurse. If growth charts are available and can be photocopied and attached to this form, you need not fill out this section.

Physical Appearance and Health

1. **Photographs of the patient's face are very helpful to us.** The best photos are ones where the face fills the photo and the patient is not smiling.

   - Are such photographs available? ____ yes ____ no
   - Are one or two included with this form? ____ yes ____ no
   - Can others be brought to the clinic? ____ yes ____ no

2. **Was the patient born with (or later discovered to have) any birth defects (things like cleft lip, congenital heart defects, club foot, etc.)?** ____ yes ____ no _____ unknown

   If yes, please describe: _____

   _____

3. **Has this patient ever had:**

	yes	no	unknown		yes	no	unknown
Allergies	_____	_____	_____	Chronic illness of the heart	_____	_____	_____
Multiple ear infections	_____	_____	_____	Chronic illness of the kidneys	_____	_____	_____
Chronic sinusitis	_____	_____	_____	Chronic illness of the joints/limbs	_____	_____	_____
Chronic hearing loss	_____	_____	_____	Chronic illness of stomach/bowels	_____	_____	_____
Visual problems	_____	_____	_____				

4. **Has this patient ever had:**

   A. Operations (since birth) ____ yes ____ no ____ unknown

Describe Operation	Surgeon's Name	Patient's Age

   B. Any other hospitalizations ____ yes ____ no ____ unknown

Reason for Hospitalization	Hospital/Doctor	Patient's Age

Neurological Issues

1. **Has this patient ever had:**
   Seizures

   ____ yes ____ no ____ suspected ____ unknown

   Type: _____

   Age when seizure(s) started: _____

   Name(s) of medication(s) given? _____

2. **Has this patient ever had a head injury leading to unconsciousness or evaluation by a doctor?**

   ____ yes ____ no ____ unknown

   If yes, please describe _____

3. **Has the patient ever had a CT scan or MRI scan of the brain**

   ____ yes ____ no ____ unknown

   If yes, was it described to be abnormal? ____ yes ____ no ____ unknown

Attention Deficit and Hyperactivity

1. **Has the patient ever been evaluated for attention deficit/hyperactivity disorder (ADD / ADHD)**

   ____ yes ____ no ____ unknown

   If yes:

   When was the evaluation done? Age: _____ Date: _____

   Was the patient diagnosed with ADD or ADHD? ____ yes ____ no ____ unknown

   Was the patient ever treated for ADD or ADHD? ____ yes ____ no ____ unknown

   What medications have been tried?

Drug	**Dose**	**Ages**	**Response**

Mental Health Issues

1. Has the patient ever been evaluated by a psychiatrist, psychologist, or MH counselor?

____ yes ____ no ____ unknown

If yes, please list each psychiatrist, psychologist and/or counselor.

A. Type of professional: _____

Reason for assessment: _____

Type of therapy (i.e., behavioral, individual counseling, group counseling, family counseling, medicine): _____

_____

Age at the time of therapy: _____ Did the therapy help? ____ yes ____ no ____ unknown

If yes, how did it help? _____

_____

_____

B. Type of professional: _____

Reason for assessment: _____

Type of therapy (i.e., behavioral, individual counseling, group counseling, family counseling, medicine): _____

_____

Age at the time of therapy: _____ Did the therapy help? ____ yes ____ no ____ unknown

If yes, how did it help?_____

_____

_____

2. Has the patient ever been evaluated for mood problems (depression, anxiety, etc.) or phobia?

____ yes ____ no ____ unknown

If yes:

When was the evaluation(s) done? Age(s): _____ Date(s): _____

3. What medications have ever been tried and how well did they work?

Drug	Dose	Response	Currently Using?

School Issues

1. List ALL schools the patient has attended and the grades of attendance:

School	City	Grades Attended	Received Special Education, Resource Room, Tutoring, etc. yes	no	unknown

2. What learning problems does the patient have?

3. What behavioral problems does the patient have?

Alcohol Exposure

Please fill in this information as completely as possible.
This information is critical to the evaluation of the patient.

Alcohol use by the birth mother

- **Before pregnancy**: Average number of drinks consumed at one time: _____
  Maximum number of drinks consumed at one time: _____
  Average number of days per week (1 to 7) that alcohol was consumed: _____
  Type(s) of alcohol: __wine __beer __liquor __unknown ___other (specify) _____

- **During pregnancy:** Average number of drinks consumed at one time: _____
  Maximum number of drinks consumed at one time: _____
  Average number of days per week (1 to 7) that alcohol was consumed: _____
  Type(s) of alcohol: __wine __beer __liquor __unknown ___other (specify) _____

Which trimester(s) did the mother drink alcohol? ___ 1st ___2nd ___3rd ___unknown

	No	Yes	Unknown
Was the birth mother ever reported to have a problem with alcohol?	____	____	_____
Was the birth mother ever diagnosed with alcoholism?	____	____	_____
Did the birth mother ever receive treatment for alcohol addiction?	____	____	_____

If the above information is unknown, please provide any information that might help describe the mother's level of ALCOHOL USE DURING THIS PREGNANCY _____

_____

_____

What is the source(s) of this information on alcohol use? _____

_____

Did the birth mother use any of the following substances during pregnancy?

Yes	No	Unknown	Type	Please List Specific Substance(s)	Month(s) of Pregnancy
___	___	___	Drugs	_____	_____
___	___	___	Tobacco	_____	_____
___	___	___	Medications	_____	_____
___	___	___	X-rays	_____	_____

Information about the Patient's Biological Parents

Birth mother's name_____ Birth date _____
First Middle Last

Mother's Race ❑ White ❑ Black ❑ American Indian ❑ Alaskan Native ❑ Hispanic
❑ Asian ❑ unknown ❑ other (specify) _____

Education level attained (last year of school completed) _____ Age at birth of patient ____

Does she have a history of learning problems? _____

When was the last contact with the birth mother? _____

Birth father's name_____ Birth date _____
First Middle Last

Father's Race ❑ White ❑ Black ❑ American Indian ❑ Alaskan Native ❑ Hispanic
❑ Asian ❑ unknown ❑ other (specify) _____

Education level attained (last year of school completed) _____ Age at birth of patient _____

Does he have a history of learning problems? _____

When was the last contact with the birth father? _____

Medical History of the Biological Family

Has anyone in this patient's biological family ever had any of these conditions? *Check all that apply*.

	Birth Mother	Birth Father
Alcoholism	_____	_____
Birth Defects	_____	_____
Stillbirths	_____	_____
Miscarriages	_____	_____
Intellectual disability	_____	_____
Other developmental disabilities	_____	_____
Learning disorder	_____	_____
Attention deficit	_____	_____
Hyperactivity	_____	_____
Epilepsy	_____	_____
Neurological disease	_____	_____
Tourette syndrome	_____	_____
Depression	_____	_____
Delinquency	_____	_____
Suicide	_____	_____
Mental health issues	_____	_____
Vision problems	_____	_____
Hearing problems	_____	_____
Chronic illnesses	_____	_____
Any specific genetic condition	_____	_____
Other (specify)	_____	_____
Other (specify)	_____	_____
Other (specify)	_____	_____
Other (specify)	_____	_____

Pregnancies of Birth Mother

1. Please list **all** the birth mother's pregnancies including miscarriages, abortions, in the order of their occurrence:

Year	Length of Pregnancy	First name of child if applicable	Live born Child yes	Live born Child no	Normally Developed yes	Normally Developed no	If not normal, please explain *Include FASD diagnosis, if known*
_____	_________	__________________	___	___	___	___	______________________________
_____	_________	__________________	___	___	___	___	______________________________
_____	_________	__________________	___	___	___	___	______________________________
_____	_________	__________________	___	___	___	___	______________________________
_____	_________	__________________	___	___	___	___	______________________________
_____	_________	__________________	___	___	___	___	______________________________
_____	_________	__________________	___	___	___	___	______________________________
_____	_________	__________________	___	___	___	___	______________________________
_____	_________	__________________	___	___	___	___	______________________________
_____	_________	__________________	___	___	___	___	______________________________

Pregnancy, Labor, and Delivery of this Patient

1. **Did the birth mother experience any difficulties during pregnancy?** __ Yes ___ No ___ Unk.

   If yes, please describe: ____

2. **Did the birth mother receive prenatal care?** ___ Yes ___ No ___ Unknown
3. **Were there complications during the labor or delivery?** ___ Yes ___ No ___ Unknown

   If yes, please explain:____

4. **Was the delivery:**_______ Natural ________ By C-section _______ Unknown

   Reason for C-Section, if performed ______________________________________

5. **What was the gravity _____ and parity _____of the birth mother**?
6. **Where was the patient born?** Hospital _____ City, State
7. **How many days did the infant stay in the birth hospital?** ____________________________
8. **Did the patient have any of the following problems while still in the birth hospital?**

	Yes	No	Unknown		Yes	No	Unknown
Feeding problems	____	____	____	Infections	_____	_____	_____
Apnea / breathing difficulties	____	____	____	Jaundice	_____	_____	_____
Supplemental oxygen required	____	____	____	Convulsions	_____	_____	_____

List of Professionals Currently Involved in Patient's Care

Primary Physician Name: _____ Phone: _____

Address: _____

Other Physicians Name: _____ Phone: _____

Specialty: _____

Address: _____

Name: _____ Phone: _____

Specialty: _____

Address: _____

Name: _____ Phone: _____

Specialty: _____

Address: _____

Mental Health Consultants *(includes Psychiatrists Psychologists, and Counselors)*

Name: _____ Phone: _____

Specialty: _____

Address: _____

Name: _____ Phone: _____

Specialty: _____

Address: _____

School Name: _____ Phone: _____

Address: _____

Contact Person *(teacher, nurse, counselor, etc.)*:

_____

Other Name: _____ Phone: _____

Profession: _____

Address: _____

Home Placements

1. List all home placements the patient has had from birth through today.

Type of placement (i.e., foster, adoptive, etc.)	Duration of placement	Age of patient when placement started

How many years has the patient been in your care? _____

Patient Trauma

Please report the age range for all traumatic events experienced by the patient. If age is unknown, place a check mark in the box if the trauma occurred.

Trauma	age range	Trauma	age range	Trauma	age range
placed out of home		sexual abuse		natural disaster	
abandonment		physical abuse		war, terrorism	
homelessness		emotional abuse		*Other (specify below)*	
food insecurity		physical neglect			
suicide attempt		emotional neglect			
serious medical issue		family death			
school violence		family incarceration			
bullying		family mental health			
serious accident		parental drug abuse			
home fire		parental divorce			
animal attack		domestic violence			

Other Details: _____

_____

What to bring to Clinic

If the patient has had any of the following assessments, please bring them to Clinic on the day of your appointment if you have copies of the results. The Clinic will also make every effort to collect this information with your consent. This information is very important to the patient's diagnostic evaluation.

_____ Facial photographs of the patient from birth to 18 years of age, without a smile.

_____ Medical records which document the problems you have reported above.

_____ School Assessments including:
- Achievement tests
- IQ tests
- Language assessments
- Social Skills assessments
- Behavior assessments

_____ Neuropsychological Assessments

_____ Developmental Assessments (birth to 3 years of age) including:
- Motor Development (fine and gross motor)
- Cognitive Development

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A Child with Fetal Alcohol Syndrome

Sterling K. Clarren, Heather Carmichael Olson, Sandra G.B. Clarren, and Susan J. Astley

Alcohol is a common human teratogen that, when ingested by a pregnant woman, can produce a wide array of fetal complications. The fetus's developing brain seems most sensitive to prenatal alcohol exposure: Alcohol-related brain damage can be quite diffuse, ranging from microcellular, neurochemical aberrations to macroscopic malformations (Stratton, Howe, & Battaglie, 1996). The neurological, cognitive, and behavior problems that arise from prenatal alcohol exposure are protean in their severity and diversity. Other prenatal determinants - for example, genetic factors or teratogenic exposures that lead to specific conditions, such as attention-deficit/hyperactivity disorder (ADHD) or learning disabilities-can further affect the developmental outcome of a child prenatally exposed to alcohol. Aversive experiences after birth and throughout life also can have a profound influence on an individual's performance in these domains. Complexity in etiology and outcome is the rule, not the exception, in working with children who have been exposed to alcohol.

Fetal alcohol syndrome (FAS) does not represent the totality of individuals exposed to alcohol in gestation or the entire group of people with impairments related to prenatal alcohol exposure. Rather, FAS is defined by specific aberrations in growth, facial form, and central nervous system (CNS) functioning (Stratton et al., 1996). FAS is noteworthy because it can be specifically identified as a condition due to gestational alcohol abuse. Thus, it is an important starting point for outreach to women who are at high risk of having other children with disabilities. In addition, this designation assists government systems related to education, social service, and criminal justice in planning for service needs.

The label *FAS* is actually less helpful for individuals who have the disorder themselves as it does not, in and of itself, guide parents or professionals in proceeding with interventions specific to the child. Moreover, the term excludes many individuals with the same degree of developmental delays related to alcohol exposure who do not have the diagnostic markers of FAS.
Nevertheless, there are two important reasons to examine whether a child's impairments are related to alcohol teratogenesis, especially to FAS. First, knowing that alcohol exposure occurred during pregnancy helps a clinician understand that if the child has a complex profile of cognitive or behavior difficulties, then alcohol-related damage may be one antecedent in a larger set of etiological factors. Children with FAS or related conditions may generally have some combination of ADHD, learning delays, language processing and usage difficulties, problems in planning and judgment, or increased soft neurological signs. In addition, if the child is school-age or older, "secondary disabilities" may have emerged form experiences of frustration, failures, and lack of acceptance by peers and adults, particularly if the full extent of the child's disability has not been recognized.

Clearly, a team approach to assessment and intervention is necessary for understanding such complex problems. A diagnosis often initiates an important spontaneous intervention by changing the attitude of family members and teachers working with the child, so they can see that the child "can't" rather than "won't" behave in an acceptable manner. Members of the child's community can then understand that the child is disabled and not simply disobedient (Streissguth, Barr, Kogan, & Bookstein, 1996).
Second, recognizing that a child has FAS may help prevent prenatal alcohol exposure in the biological mother's future pregnancies. In an assessment of FAS, both the biological mother and her child are the focus of the team's efforts. Women who have children with FAS usually drink regularly and in high volume during pregnancy. Although it is true that women who consume alcohol in the gestation period may by committing "fetal abuse", the case of a woman drinking purposefully during pregnancy to harm her child is rare. It is therapeutic to inform biological mothers of this problem so that they know that the child is receiving appropriate supports and everyone can proceed in a positive manner. Although the process of working with the biological mother can be complex and involves a different group of professionals than those needed to assess the child, it is critical and ethically necessary that these

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diagnostic and intervention efforts be linked (Astley, Bailey, Talbot, & Clarren, 1998).

ASSESSMENT FOR DIAGNOSIS OF FETAL ALCOHOL SYNDROME

The features of FAS are not dichotomous (present or absent) but, rather, each feature is on a continuum from clearly within the normal range to clearly the feature of FAS. Without suitable guides and standards, this leads clinicians to variable judgment in final diagnosis. To minimize clinical variability, the diagnosis of FAS or related conditions is made using a sequence of four 4-digit Likert scales (Astley & Clarren, 1997) in the clinics of the Washington State FAS Diagnostic and Prevention Network. Delays in growth, facial morphology, organic brain damage, and teratogenic exposure to alcohol are each evaluated separately. A "1" on any scale means a finding within the normal range. A "4" on any scale represents a finding that corresponds with accepted cases of FAS. A score of "2" or "3" specifically defines intermediate steps between clearly typical and atypical. It is important to note that these scales do not necessarily measure increasing severity; rather, they are scales of greater clinical confidence that the sought FAS characteristic is present. A child with a "4" for brain damage, for example, meets the medical criteria for a structurally altered brain but may be more cognitively or behaviorally within the normal range than a child with a score of "2" in whom the etiological relationship between brain structure and brain function is diagnostically indeterminate. Similarly, a child with a "4" for facial morphology has all of the facial diagnostic features of FAS yet may be somewhat more attractive than child with a score of "2"-who has an unusual face, but not the facial features common to FAS. The final category based on examination of the child is whether he or she has delayed growth. Establishing if a person's height or weight is "blunted", due to prenatal reasons, from its genetic potential is actually the most difficult part of diagnosis. Growth retardation is defined as a "4" when a child's measurements are less than 2 standard deviations (SD) from the mean after height (adjustment for mean parent height) and for weight.

The alcohol exposure scale is judged by whether the dose exposure pattern approaches on that causes fetal damage in animal models and whether the information is documented or speculative. Dose response relationships between maternal alcohol intake and fetal outcomes remain complex and somewhat vague for various reasons. Obtaining accurate information on alcohol intake during pregnancy is difficult because it is almost always recorded in retrospect, with the potential problems of the mother's poor memory or denial. Many maternal and fetal factors also play key roles in determining if any specific dosing pattern is damaging to that individual. In the majority of animal studies in multiple species, it has been necessary to give high dosage exposures, with peak blood alcohol concentrations (BAC) in the 100-200 milligrams per kilogram (mg/kg) range, and to deliver them at least weekly for the first several weeks of pregnancy. Even these high doses are not uniformly teratogenic; they are "high risk". When women report consumption likely to cause drunkenness (an approximate BAC = 100 mg/kg or higher) on a weekly basis, this is considered a "4". Any other pattern of definite exposure is judged a "3" because no dose is guaranteed to be absolutely safe.

The term FAS applies to children who have all "4"s or combinations of at least two "4"s and no more than two "3"s on the four scales. Other scores are converted to words in combinations of the descriptive terms: sentinel physical findings; static encephalopathy or neurobehavior disorder; and alcohol exposed, alcohol unexposed, and alcohol exposure unknown. A full explanation of this approach and its diagnostic terms as well as a method for judging the importance of these comorbidities, are available in the *Diagnostic Guide for Fetal Alcohol Syndrome and Related Conditions* (Astley & Clarren, 1997). The fetal alcohol diagnosis must be considered in the context of other prenatal and postnatal factors that contribute to the unique findings for each individual.

CASE STUDY INVOLVING AN INTERDISCIPLINARY TEAM ASSESSMENT

The FAS clinic team is comprised of individuals who help collect and interpret the data needed for diagnosis, assist in developing a comprehensive intervention plan, or both. Professionals are needed

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from the disciplines of medicine, psychology, speech-language pathology, occupational therapy, social work, public health nursing, and family advocacy. It is also helpful to have a staff epidemiologist who can create data forms and databases and direct clinical research efforts based on these data.
The remainder of this chapter presents the composite case of Anna, a child with FAS. This case illustrates the following steps in the diagnostic interdisciplinary team process: 1) preliminary team conference; 2) team assessment, including caregiver interview, physical examination of the child, and assessments of the child by occupational therapy, speech-language pathology, and psychology team members; 3) team deliberation; 4) case discussion and feedback to the parents; 5) additional case discussion and a therapeutic debriefing with the parents; 6) further case discussion and a therapeutic debriefing with the child (when appropriate); and 7) staff debriefing. Beside preserving patient confidentially, employing a composite case permits discussion of a combination of FAS characteristics that would not necessarily be found in any one case. Exploring the case of a primary school-age child allows a more extended developmental perspective. It also sensitizes the reader to the full scope of difficulties that children with FAS have by the time they reach elementary school, which generally are not clear in preschool. Overall, although Anna is fictitious, she presents the typical challenges in FAS diagnosis, treatment, and family support.

Record Review and Preliminary Team Conference

Anna's adoptive parents initially called the FAS clinic for an appointment. The family had been referred to the clinic by Anna's teacher, who had taken a workshop on FAS, and by her physician. As is frequently the case, Anna's doctor had not previously considered an alcohol-related diagnosis but agreed to the assessment when Anna's parents sought his advice (Clarren &Astley, 1998). The family had been sent an extensive intake form. This form was specifically designed to obtain historical data from the family that would help the clinic team reach a fair and complete conclusion. These data included 1) growth records; 2) childhood photos; 3) medical records of congenital abnormalities; 4) neurological problems and ongoing health issues; 5) previous evaluations of cognition and behavior; 6) reports of response to psychotropic medication; 7) specific documentation of alcohol exposure in pregnancy; 8) exposure to other drugs or additional complications during pregnancy; 9) academic problems or cognitive delays of the biological parents or their families; 10) a general overview of the family's genetic background; 11) reports of multiple placements and issues of caregiver attachment; 12) abuse or neglect; and 13) a general record of problems or difficulties with family, peers, and school. This intake form is available in the *Diagnostic Guide for Fetal Alcohol Syndrome and Related Conditions* (Astley & Clarren, 1997).

At the preliminary team conference, these extensive past records were reviewed, and the following summary was presented to the clinic staff by the physician and psychologist. Anna was 8 years and 1 month old. She was born to married, Caucasian parents when her mother was 28 years of age and her birth father was 35 years old. This was the third live born infant for Anna's birth mother. Her pregnancy was complicated by extensive alcohol use. The birth father reported that he would generally buy one case of beer daily and that when it was available he and his wife would each drink about half of this amount in the evening. This level of drinking persisted through the first half of the pregnancy. During the second half of Anna's gestation, Anna's birth father drank more while her mother drank less, although she still probably ingested about a six-pack daily until delivery. Anna's mother also used marijuana about once a month and smoked half a pack of cigarettes each day. The pregnancy was further complicated by physical abuse of the mother by her husband, although this abuse never led to a medical assessment during the pregnancy. Both biological parents reported that their own fathers, but not their mothers, had been heavy drinkers. Neither biological parent reported significant academic problems, and both had finished high school.

Anna was born at term, and her delivery was described as typical. At birth, she weighed 2.2 kilograms (kg) and her length was 44 centimeters (cm). Anna was always described as small. While in foster care, Anna received a nutritional evaluation and a thyroid screen. Anna grew steadily but more slowly than

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typically developing children. One previous foster parent repeatedly asked her physician to hospitalize the infant because she ardently believed that her inability to "fatten the baby up" meant that the baby was ill. Anna had an inguinal hernia that was repaired when she was 9 months old. She had chronic problems with otitis media until she reached age 3, though she never had a documented hearing loss. Despite these problems, she had been in good health overall.

After Anna was born, she lived with her parents for about 6 months, then she was removed from parental custody after the biological mother was several beaten by her husband. In addition, investigators found that the child was living in an unclean apartment without food or appropriate clothing. Six month-old Anna was placed in foster care and moved periodically over the next two and a half years while social service agencies determined that neither parent could control their drinking and regain custody. Anna was then made available for adoption and was retained by her last foster family (mother, father, and a brother 3 years older than Anna) when she was about 3 years of age. The adoption was legalized when Anna was almost 5 years old.

At the time of the clinic visit, Anna's adoptive parents reported that she had shown behavior problems since 30 months of age. Sometimes Anna was very negative and aggressive, especially with family members, while at other times she was cooperative and pleasant. Upon entering preschool, she was reported to be quiet but soon showed qualities similar to those observed at home. In fact, she was so aggressive with her peers that she was unsuccessful in two preschool programs. Her parents said that these behavior problems continued but had grown less frequent and violent since Anna started kindergarten.

Anna was evaluated by a developmental pediatrician at 6 years and 11 months of age, and she was diagnosed with severe ADHD. Anna was placed on methylphenidate but had an unanticipated response with a dramatic increase in irritability. Her parents stopped giving her the medication. Anna's reaction distressed her whole family, and her parents declined to try other medications, but they did attempt to reduce the amount of sugar in her diet with no apparent positive effect. A psychiatric evaluation produced a further diagnosis of oppositional defiant disorder, and Anna was described as "anxious".

At age 7 and midway through first grade, Anna was made a "focus of concern" by her school district because of poor academic progress and increasingly problematic behavior. As part of her school assessment she was evaluated using a standardized test of intelligence, the Wechsler Intelligence Scale for Children-Third Edition (WISC-III; Weschler, 1991). On that test, her verbal IQ score was a standard 68 (below expectations), and her performance IQ score was a standard 90 (within normal limits). A fullscale IQ score was not calculated because of the discrepancy between Anna's verbal and performance scores. Factor scores in the areas of verbal comprehension and freedom from distractibility revealed significant difficulties while Anna's factor score in the area of perceptual organization was in the lowaverage range. On an individually administered academic skills measure, the Woodcock-Johnson Test of Achievement-Revised (Woodcock & Johnson, 1989), Anna received the following scaled scores: Broad Reading (75), Broad Mathematics (71), Broad Written Language (80), and Broad Knowledge (86). Her standard score on the Vineland Adaptive Behavior Scales' (VABS; Sparrow, Balla & Cicchetti, 1984) Adaptive Behavior Composite was 52, and the subdomain scores were Communication (50), Daily Living Skills (45), and Socialization (64). School district recommendations were to provide resource room assistance given her ADHD diagnosis, but no specific educational plan was developed to address her cognitive and academic difficulties.

At the time of the FAS assessment, Anna's adoptive parents were confused and exhausted. They wished to understand how Anna's multiple diagnoses related to each other and how to maximize the effectiveness of her academic and mental health interventions.

Team Assessment

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The FAS clinic evaluation included an hour-long interview of Anna's adoptive parents and several assessments of the child (whose chronological age was 8 years and 1 month), which included a physical examination, an occupational/physical therapy assessment for soft neurological signs and fine motor problems, a specialized speech-language evaluation, and a limited amount of additional psychological testing. The goal of conducting these assessments was not necessarily to evaluate the full extent of Anna's development. Rather, it was to gather sufficient information to reach a diagnostic conclusion regarding the diversity and nature of her developmental functioning.

Caregiver Interview

A team physician and psychologist conducted an interview with Anna's adoptive parents. The interviewers guided the session to determine if Anna had the related conditions and functional impairments common in case of FAS. These questions probed the arenas of planning, behavior regulation, abstract thinking and judgment, information processing and verbal memory, spatial skills and memory, social skills and adaptive behavior, sensorimotor integration, and both oral-motor and motor control skills.

Anna's parents seemed appropriately concerned but confused about the many previous assessments of their daughter that had apparent nonoverlapping diagnoses. They commented that they sometimes understood the antecedents of her angry outbursts (but often did not) and that Anna was basically loving and caring. Nevertheless, Anna had never enjoyed being held or hugged for more than a brief period time. Furthermore, her parents said that she had always been very sensitive to loud noise and to rough or scratchy clothing.

Anna's parents noted that their daughter had difficulty organizing spaces; for example, she tended to crowd the letters of her name into one corner of a page and she could not put her toys away in their proper places. Her parents also agreed that their daughter had tremendous difficulty following directions. They reported that she generally failed to remember an instruction if more than a few minutes elapsed between the time the instruction was given and when she was expected to carry it out. Anna also could not successfully follow more than a one-step instruction. She could repeat instructions if she practices saying them many times (e.g., Question: "Anna, what do we do before we eat?"; Answer: "We was our hands"). Yet Anna usually forgot the rule without a direct reminder at the time the instruction was to be implemented. In fact, she did not understand lengths of time (e.g., the difference between an event taking place in a few minutes or one that was a few days away).

In the domain of social skills, Anna's parents described her as isolated with no friends. She seemed to enjoy the company of other children but often tried to direct all activities. This behavior usually led to marginalization by her peer group. When rejected, Anna sometimes played alone, but she usually responded to peer rejection or noncompliance with anger or physical aggression. Anna played well with younger children (ages 3 or 4 years) and was kind to animals.

In physical terms, Anna had trouble going to bed and often awoke in the night, but then she generally tired during the latter part of the day. Her mother commented ruefully that Anna could climb, in-line skate, and do other age-appropriate outdoor activities but did them in a frighteningly reckless and somewhat clumsy way. In general , Anna was described as having problems with self-regulation. Her parents had learned to send their daughter to her room when she was out of control. In time out, Anna quickly calmed down and seemingly forgot the entire event within minutes. Such outbursts could occur daily or even several times per day.

During the interview, Anna's parents confirmed the history of alcohol exposure that had been reported to them by the biological father. Apparently, Anna's biological mother had been in recovery at the time of the adoption and had given the adoptive parents the same facts. Anna's adoptive parents thought her biological mother was still living in the area and was once again drinking. They had not been in contact with her for several years.

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Pediatrics

The results of the physical examination conducted by the team physician revealed that Anna's height was 115 cms, her weight was 18k kgs, and her head circumference was 48.5 cms. The three facial features that defines the dysmorphic face of FAS were each carefully assessed. Her palpebral fissures (the horizontal length of the eyelid slit opening) measured 2.3 cms. Her philtrum (the vertical furrows between the nose and border of the red portion or vermilion border of the upper lip) was judged to be "flat" when compared to standard photos of philtrums of variable fullness. Similarly, the vermilion border was judged to be "very thin" using the photographic guide (available in the *Diagnostic Guide for Fetal Alcohol Syndrome and Related Conditions* [Astley & Clarren, 1997]). In addition, Anna had a small jaw and a mild overbite of her new secondary upper incisors. The rest of Anna's physical examination was unremarkable.

Occupational Therapy

Fine and gross motor skills were within normal limits using the Bruininks-Oseretsky Test of Motor Proficiency (Bruininks, 1978). Although Anna's parents had concerns about "clumsiness," that problem was not identified with this tool. The Quick Neurological Screening Test-Revised (QNST-R; Mutti, Sterling, & Spalding, 1978) was also administered. This tool is generally more useful to screen multiple areas of neuromotor integration and soft neurological signs. A normal score is less than 20; an abnormal score is more than 50. Anna's score was 45, in the "suspicious" range. Particularly difficult for Anna were coordinating rapid controlled movements, balance, and tasks involving spatial awareness of her body. These results fit with findings on the Beery-Buktencis Developmental Test of Visual-Motor Integration (VMI; Beery, 1997), signifying that Anna had below-average abilities in figure copying and a very disorganized approach to more complex visual information. A short sensorimotor history questionnaire completed by Anna's adoptive parents revealed sensitivities to tactile and auditory information, echoing descriptions from the caregiver interview. This sort of nonstandardized checklist is used in FAS clinics when there are concerns about sensory processing.

Speech-Language Pathology

Impairments with language, cognition, and social behavior are not unusual for children with FAS and related conditions, and they underlie difficulties in social competence and some aspects of academic performance. Research measures of social communication and social reasoning are used in FAS clinics to tap this common area of concern, and the results these measures produce capture something of the day-to-day problems that parents of children affected by alcohol describe. In addition, age- and developmentally appropriate standardized measures of receptive and expressive language are also employed in clinics to conduct a brief assessment of language development.

Anna's receptive and expressive language skills were broadly within the typical range; she nonetheless showed notable delays in storytelling and mental-state reasoning, two aspects of social communication and social reasoning. Anna was asked to retell a story she had just heard, suing a picture book without words as a cue. Anna's narrative was vague and poorly connected; in effect, she described elements in each picture without linking them into a story line. She could not take her listener's perspective into account in communicating the story. Anna understood the facts of the story but could not mentally "step into another person's shoes" when asked questions that required understanding another person's perspective. In these tasks, Anna did not give clear evidence that she understood what other people were thinking. These observations were congruent with reported information from the caregiver interview.

Psychology

As is often the case, the clinic was provided with valid and relatively recent testing by school and community professionals. To supplement these data, Anna was given the core assessment from the NEPSY, a Developmental Neuropsychological Assessment (Korkman, Kirk, & Kemp, 1998), a standardized battery of tasks that provides a developmental neuropsychological assessment for children ages 3-12 years. Anna's scores on the test's Core Domains of Language and Sensorimotor Function were low-average while visuospatial processing was in the borderline range. She scored well below average

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on Attention/Executive Function and Memory and Learning. Her scores on individual subtests were uneven and provided considerable insight regarding her problem-solving and learning styles. Of particular interest was Anna's very poor performance on a narrative memory task similar to one given in the speech-language assessment. In this task, which resembles school activities, the child listened to a story read aloud, attempted to tell it on her own, and then answered comprehension questions. Again, Anna's version of the story was vague and sparsely detailed. Even when cued, Anna often could not always remember the information offered in the story. When asked a question she often started to give an answer, then seemed to lose the aim of the task, and finally made unrelated responses that suggested she was guessing just to give an answer. She appeared very anxious during this task, shifting around in her chair, commenting on noises outside the room, and asking whether the testing was almost done.

To provide an estimate of behavioral function, Anna's adoptive mother completed the Child Behavior Checklist for 4- to 18-year olds (CBCL; Achenbach, 1991). Her second grade teacher completed the Teacher's Report Form (TRF; Achenbach, 1991). Parent report on the CBCL revealed overall behavior difficulties, with a Total Behavior Problems T score of 79, which is within the clinically significant range. The realm of internalizing problems was also clinically significant due to an elevated score suggesting anxiety. Externalizing behavior problems were also rated in the significant range, with elevated scores on scales of aggressive and "delinquent" behavior as well as difficulties with thinking, social skills, and attention span. Anna's Total Competence T score was 32, falling below the clinical cutoff, with poor scores on scales of social and school competence. This resonated with the mother's concerns about her daughter's inability to learn right from wrong: Anna sometimes attempted to hurt family members, yet she had a sense of humor and the ability to be loving and caring.
On the TRF, Anna's teacher expressed concern about behaviors in both Internalizing and Externalizing scales. Again, Anna's overall Internalizing problem score was elevated primarily because of her anxious behavior. Her Externalizing behavior problem score was elevated mostly due to her overactive and aggressive behavior. Anna's teacher reported that the child would destroy her own and others' possessions when angered. However, her rating showed that she could occasionally work hard and seem happy. Overall, Anna's teacher's ratings also indicated that her student was having some difficulty behaving appropriately and learning. She noted that Anna did better in small, highly structured environments than in the larger classroom setting. The teacher thought that Anna was very hard on herself, with very high expectations and a tendency to become very upset (even self-abusive) if she did not meet her own expectations.

For many children in the FAS clinic, only brief screening is carried out by the psychologist to supplement available test results from community professionals. For children who are old enough and have sufficient intellectual capability, the child and adult versions of the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1994) and the Rey Complex Figure Test (RCFT; Meyers, Meyers, & Kelly 1995) are highly informative. Used together these tools assess verbal learning and memory, nonverbal memory and visuospatial skills, the child's ability to organize hi or her behavior toward a complex end, and his or her behavior when carrying out demanding tasks. Literature on fetal alcohol effects suggests these might be areas of concern for individuals affected by prenatal alcohol ingestion. Findings from the CVLT and RCFT are often supplemented by several informal drawing tasks and a short interview. For children from preschool to late elementary school age, behavior observations are often carried out while the child is receiving the physical examination or other on-site testing and when the child is in an unstructured, highly stimulating environment (e.g., in the waiting room, on an elevator ride, during a walk through the building). Because a formal adaptive behavior assessment is often not part of a child's file, the psychologist will sometimes give the Summary Version of the VABS (Sparrow et al., 1984) prior to the caregiver interview.

Team Deliberation

Anna met the criteria for FAS in that she had been exposed to alcohol and had confirmed growth delays, specific atypical facial features, and evidence of CNS dysfunction. Details for these and other factors are

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provided as follows:

Growth
Anna's growth was considered definitely atypical, as her height and weight were both below the 3rd percentile after a height adjustment for mean parental height. Anna's height of 155 cms was at the 2nd percentile. The height of her biological parents averaged 174 cms. Adjusting for mid-parental stature determined that Anna was actually 3 cms smaller than would be predicted from her genetic background. Therefore, her atypical growth pattern was independent of her genetic background.

Dysmorphology
Those with FAS have short palpebral fissures ("short" when more than 2 SD below the mean) and a flat philtrum and thinned vermilion border. The philtrum and lip must each be judged a "4" or "5" on a 5-point rating scale in comparison to a standard set of five photos. Anna's palpebral fissures were measured at 3.5 SD below the mean. Her lip was judged a "5" while her philtrum was given a rating of "4". Her dental malocclusion, although not of relevance to the FAS diagnosis, was a common associated finding. Overall, she had the distinctive facial features that characterize FAS.

Central Nervous System Dysfunction
Evidence for CNS dysfunction can be defined structurally, neurologically, or by examining psychometric evidence. Anna had positive findings in all of these areas. Her head circumference was below the 2nd percentile. By itself, microcephaly is a sufficient finding for FAS diagnostic purposes, but Anna also had an atypical neurological exam, with a QNST score about the usual cutoff and evidence of visual-motor difficulties on the Developmental Test of Visual-Motor Integration. Anna's behavior was characterized by severe ADHD, adaptive behavior problems, clear social-communication impairments, a learning disorder, a significant verbal-performance discrepancy shown in IQ testing, and evidence of memory and attention/executive function problems in neuropsychological assessment. The descriptive diagnostic term *static encephalopathy*, with evidence of diffuse CNS dysfunction, applied to Anna.

Alcohol Exposure History
The history of alcohol exposure in utero was judged to be definite, as it was independently confirmed by both birth parents. Consumption of 6-12 beers or more, on a daily or nearly daily basis, would place a fetus at definite risk for damage due to alcohol exposure.

Comorbidities
There were no additional physical findings, problems in the genetic background, or other teratogenic exposures that suggested an alternate or additional prenatal etiological diagnosis. Based on record review, interview, and behavioral observations, the team was in agreement with the psychiatric diagnoses of oppositional defiant disorder and moderate anxiety. In part, these conditions were hypothesized by the team to be situational, arising from Anna's prolonged frustration from criticism by others as well as herself regarding her poor performance. In other words, these would be secondary disabilities.

Recommendations
After discussion to establish the diagnosis, the team began to develop a tentative list of recommendations to be shared with the family during the case conference. It is useful to divide suggestions into at least four categories: medical, mental health, formal/informal education, and social services. In certain cases, additional categories (e.g., legal, correctional) are needed.

Medical
Anna had a classic presentation of FAS. No further specific medical diagnostic evaluations were necessary in this case. However, this is not always the case. Individuals with prenatal alcohol exposure can have alcohol-related and other conditions or simply alternate conditions. Differential diagnosis often need to consider relatively common genetic conditions like fragile X syndrome or Turner syndrome as

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well as obscure dysmorphic syndromes of genetic or alternate teratogenic cause. Any FAS program must always be alert to the possibility of alternate diagnoses involving other syndromes.

Another noteworthy medical issue was that there was a strong history of family alcoholism. Both of Anna's parents and her grandfathers were alcoholics. Thus, there was a chance that Anna carried a genetic propensity for alcoholism independent of her condition of FAS. The team felt that Anna would need clear and regular warnings throughout childhood and adolescence that drinking could cause her to become an alcoholic. Such direct messages help some children withstand peer pressure to begin alcohol use in adolescence.

In addition, Anna was small but had consistently grown parallel to typical parameters. This fact, along with her generally unremarkable physical examination, meant that there was no reason to recommend further medical evaluation of her growth. (Intriguingly, many children with FAS have a robust growth spurt at the time of puberty, moving in the typical range for height at that time.) On this note, it is not surprising that Anna's physician had not considered FAS diagnosis or referral, because Anna's physical health was good and her problems were in areas not usually considered as health care problems.

Mental Health

Anna had clinical evidence of distractibility and inattention and had had an unexpectedly adverse reaction to methylphenidate. At the time of the clinic visit, it remained possible that Anna fit the diagnostic criteria for ADHD within broader diagnosis of FAS. Thus, Anna might still respond to methylphenidate prescribed at a lower dose or to an alternate stimulant medication. It was also possible that her inattention and distractibility were due to anxiety and could be resolved if her anxiety and other problems were addressed, perhaps with an alternative, nonstimulant pharmacological approach as well as situational remediation.

Some families are concerned by the use of medications with children already affected by prenatal alcohol exposure. It was important that Anna's family be reassured of the general safety and potential benefits of medications. Nevertheless, the team felt it better for Anna's overall emotional state to be judged and the adjustments in her educational program and family expectations to be evaluated before further drug trials. Based on the outcome of such monitoring, a psychiatrist might then be better able to prescribe psychotropic medications.

Making those additional changes would be difficult. Anna's parents were already frustrated and fatigued by caring for a child whose behavior problems had escalated while her adaptive function had declined. Anna demonstrated complex cognitive and behavior impairments. Managing the child's behavior and helping her to learn would require expert assistance. The team decided to encourage Anna's parents to work with a counselor in developing appropriate parenting strategies and addressing the stressed inherent in raising a child with FAS. However, it is difficult to find such counselors and to fund this type of ongoing counseling assistance. If the parents did find a counselor, the team felt it would be ideal if that person or Anna's psychiatrist functioned as a service coordinator. The case management goal would be to align home and school behavior programs, with dual foci on eliminating aggressive behaviors and building anger management and socialization skills.

Another possible source of assistance was parent networks. Such support groups are remarkably useful resources for families raising children with FAS. In the 1990s, parents increasingly began joining together to support and educate on another, to advocate for funding and missing services, and to promote societal recognition of and research on FAS and related conditions. The team planned to augment the parents' access to information and self-help advice by providing them with a telephone hotline number for FAS and copies of recent issues of FAS community education newsletters.

Formal/Informal Education

In some states, Anna would qualify for special education under the category of "health impaired" given

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either her diagnosis of FAS or of ADHD. She might also qualify as "neurologically impaired" based on microcephaly coupled with atypical neurological findings of fine motor delays and a significant number of soft neurological signs. In addition, Anna could qualify as "learning disabled" because of her psychological evaluation. Anna clearly met the criteria for, and needed, an individualized education program (IEP).

Most school districts have an approach to children with complex needs, such as Anna, that involves special education classes or resource room help for academic work; supplemental speech-language, occupational, and physical therapy services; and inclusion with typically developing peers during certain activities (e.g., recess, lunch, library time). These qualifying children may also be accompanied by a paraeducator for a portion of or the entire school day. This general plan seemed reasonable for Anna, although her pattern of special needs did not completely fit interventions such as those designed for children with mental retardation, learning disabilities, or severe behavior disorders. Therefore, individualized and flexible intervention planning at school was needed. Based on Anna's profile of test results, specific classroom techniques included 1) repeating practice of learning materials; 2) using less abstract materials; 3) limiting the need for Anna to remember spatial information; 4) breaking long instructions, stories, or lessons into smaller parts; 5) encouraging Anna to work slowly and carefully; 6) allowing time during transitions for Anna to become self-motivated and interested in the next activity; 7) analyzing strategies Anna used on her own during learning activities and offering more effective strategies as appropriate; and 8) informing Anna when she was doing well by rewarding effort and not achievement.

The team felt that Anna would benefit from occupational therapy services designed to assist her in better modulating incoming stimuli and to decrease performance anxiety by altering her classroom environment. If occupational therapy services could be provided at school, a private occupation therapist might be a useful addition to Anna's service team. Finally, speech-language consultation was recommended to enhance Anna's social-communication skills.
Furthermore, Anna would benefit from participation in extracurricular activities that she enjoyed and did well. Such activities could help raise her self-esteem and would be less likely to promote performance anxiety. Nevertheless, it was important to emphasize that Anna should only be enrolled in activities supervised by adults accustomed to working with children with special needs.

Social Services
At the time of Anna's adoption, fetal alcohol effects and the possibility of a lifelong disability were not raised with the family. Given the documented history of voluminous alcohol exposure during gestation and the history of growth problems from birth, the team believed that the issue of FAS should have been evaluated at the time of adoption. It would have been reasonable then to offer a subsidized adoption to offset added educational and mental health services that Anna would probably need. The team recommended that this issue be revisited with the appropriate social service agency. Subsidized adoption should include medical coverage, psychiatric benefits for the future if preapproved, and a monthly cost supplement. In addition, because Anna had permanent disabilities, she should qualify for Supplemental Security Income (SSI) coverage. As a child, eligibility is based primarily on functional ability, and the receipt of benefits is dependent on parental income. The issue of SSI funding could be reexamined later when Anna neared adulthood. The Division of Developmental Disabilities was another agency to contact for possible resources or benefits. The agency has strict qualifying criteria, but this option was worth pursuing.

Case Discussion: Feedback to Parents

The case discussion actually occurred in two phases. The first part consisted of elements typically discussed with parents during an assessment feedback session. The second phase, however, was a unique feature of the particular clinic that evaluated Anna.

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Part I

Diagnosis and treatment recommendations were shared with Anna's parents in a roundtable forum. Each team member who had tested Anna briefly stated his or her specific findings, gearing discussion of test results to support the recommendations that would be mentioned later. For example, the physician articulated the medical diagnosis of FAS, and then the occupation al therapist, the speech-language pathologist, and the psychologist who had tested Anna all stated their findings. The psychologist who interviewed the family then gave the team's recommendations in broad outline. All feedback was provided with careful sensitivity to the parents' emotional state and apparent level of comprehension.

In this large group setting, with all team members and some observers, the parents appeared fairly composed and quietly accepting of the diagnosis and intervention ideas. Nonetheless, their emotional responses were complex. On one hand, Anna's parents seemed pleased and relieved to receive an overall explanation for Anna's primary problems. On the other hand, they were troubled that Anna's complex neurological problems and her reactions to the accompanying difficulties had not previously been made clear. They also felt despair because they believed they had floundered for so long in caring for their daughter. Finally, they mentioned some fleeting anger at Anna's biological mother for causing these problems.

Part II

At this particular clinic, after clients have discussed the situation with the whole team, they have a quiet time when they can talk privately with one person on the team, usually the psychologist involved in the initial interview. This final phase with the caregivers provides a time for parents to catch their breath, express their feelings about the events of the day, and share their reaction to the diagnosis. Thereafter, they can hear and discuss the diagnosis and recommendations again to clarify their understanding and to begin initial planning for interventions based on clinic referrals. This final period honors the caregivers' and child's needs for a limited emotional closure to a stressful experience and for a way to review the many concepts and ideas they have just heard. Families often report how important this final time of consolidation is for them.

Anna's parents had endured an emotionally intense morning. At this second phase of the discussion process, the psychologist asked, "How are you doing? Does Anna's diagnosis make sense to you?" Then she waited and listened. Tears welled up in Anna's mother's eyes; her father let out a deep sigh. Finally, the father said how hard it was to hear that Anna did have FAS. The mother said she thought all along that Anna had FAS; Anna was so like the descriptions she had read. However, she kept wishing she would wake up and Anna would be just like her cousins and the kids next door. But now the mother knew Anna would never be an ordinary little girl, teenager, or adult. For several minutes the parents quietly cried, but they eventually regained their composure. The psychologist expressed her support. Then, Anna's mother asked what the family's next step should be.

The psychologist began to help the parents make sense of the diagnosis and recommendations. The psychologist read the diagnostic information and suggestions aloud to the parents to make sure the wording was clear and sufficiently informative. She clarified the meaning of a diagnosis of FAS. Using schematic drawings and straightforward descriptions the psychologist reviewed the word syndrome and each of the three basic aspects of the fetal alcohol syndrome: growth, facial features, and organic brain damage. She discussed how Anna met the growth criteria, as she had always been small, and her height and weight measurements during the assessment were below the 5th percentile compared to those of her peers. The psychologist explained the importance of small eyes and a thin upper lip and philtrum as physical markers for FAS and briefly described the embryology of these features. She also pointed out that Anna was a very pretty child and these facial characteristics did not stand out or negatively affect her looks. Then the psychologist explained the organic brain damage portion of the syndrome and how Anna demonstrated this characteristic. This was the time when the old and the new test data were analyzed. The parents asked many questions, and time was given to explain to them how Anna's profile of test results related to her learning and behavior problems. In particular, the results of the QNST,

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which had indicated an atypical pattern of neurological soft signs and motor weaknesses, and her low scores on adaptive problem solving on the VABS were reviewed because both lent support to the finding that Anna was functioning at the level of a child half her chronological age. Also, her limited linguistic understanding of another's point of view and the discrepancy between her verbal and average nonverbal reasoning were discussed to help the parents understand why Anna seemed well adjusted at one moment and then had such great difficulties and frustrations the next.

Specific telephone numbers were provided, and referrals to three possible counselors/behavioral consultants were made. The parents also signed a mutual exchange of information form so the psychologist could talk to Anna's teacher and school counselor at a future date. In addition, the psychologist provided handouts from the resource box of articles on FAS, copies of the most recent newsletters, and ordering information for books that might be of value to Anna's teachers.
The psychologist next asked if the parents thought Anna needed to talk about the diagnosis, and the parents said they did not think she would understand. To Anna, this day of testing was similar to her assessment process at school. In the future, they thought they could explain her diagnosis or they would contact the clinic for assistance. As a rule, feedback is given to an older child, a teenager, or an adult. If the child is briefed, there are several topics that generally should be considered for discussion with the child and the caregivers together. The feelings the child or caregivers may have about the biological mother's role and the frustration of ongoing problems in learning, behavior, and growth need to be recognized. The team should emphasize that they know the child works hard but has difficulties and may have been misunderstood over the years. In addition, the professionals need to clarify that the diagnosis explains why learning and being calm have been hard. Also, the child must be encouraged that he or she can learn and work but may need extra time and assistance. Again, the child also needs to be informed of his or her risk of becoming alcoholic. Finally, definite closure of the team assessment has to be made. This is the time to determine if the child requires follow-up with the clinic. In Anna's case, the psychologist closed the session by expressing her appreciation to the caregivers for their courage, good parenting, and cooperation as well as acknowledging how difficult the process had been. She stated she would be available to telephone Anna's teacher if necessary. Then the psychologist walked to the area where Anna was playing and shook the child's hand, told her what a good job she had done, and thanked her for coming to clinic.

CONCLUSION

The reader may wonder why a school-age child was used as a case example when the primary focus of this book is assessment in the early childhood years. Although younger children are assessed for FAS and related conditions, an older child's case demonstrated the richness and complexity of the accompanying performance problems that are not well described or measured until elementary school. Yet early diagnosis is important. It is likely that proper planning will reduce secondary disabilities and perhaps even improve cognitive performance when a diagnosis is made at the earliest possible time. Furthermore, the younger the child at the time of diagnosis, the more probable it is that the biological mother is still of childbearing age and would ingest alcohol during future pregnancies.

Unfortunately, the diagnosis of FAS cannot always be established conclusively in young children; even if the diagnosis is established in the preschool years, it is rarely clear what specific cognitive and behavior problems will follow. After all, the diagnosis of FAS relies on independent evidence of growth delays, a cluster of specific atypical facial features, organic brain damage, and a history of prenatal exposure to alcohol. The physical findings of poor growth and facial alteration and the history of alcohol exposure can all be fairly assessed in preschoolers, but detecting subtle levels of brain damage is much more problematic. If the child has microcephaly, hard neurological signs, or has had a brain image that discloses structural aberrations, this component of the diagnosis can be confirmed. If these observations are typical, alcohol-related brain damage could still be present at a microscopic level that can only be detected with late 20th century clinical techniques through a battery of psychometric testing. Reliable and valid testing of this type is not available for very young children. Furthermore, even if the diagnosis

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can be established through physical observations, the child's functional problems could be wide ranging and only well understood through formal assessments done over several subsequent years. As of 2000, there is no solid evidence that the facial characteristics and growth delays in children with FAS predict that there will be definite brain impairments or any specific level of delay. These findings cannot be used as proxy measures for brain performance itself. For infants, toddlers, and preschoolers, a senorimotor history questionnaire, developmental screening (e.g., the Bayley Infant Neurodevelopmental Screener [Aylward, 1995] or the Miller Assessment for Preschoolers [MAP; Miller, 1988]), and observation of parent-child interactions are often carried out by the FAS clinic occupational therapist and psychologist working together. Although these assessments are useful, they can rarely predict the types of processing difficulties that are at the heart of the ongoing FAS disability. Anna was noted to have had problems with anger and socialization in preschool although the cause was not understood at that time. Actually, many children who are later found to have significant cognitive and behavior problems seemed, to both their parents and teachers, to be developing typically before the age of 4 or 5 years.

As of 2000, the approach to the problem of FAS diagnosis in young children is twofold. First, the most complete assessment possible is conducted along the lines discussed in this chapter. Then the interdisciplinary team assesses the risk factors of each client (i.e., the biological mother and the child). If the mother drank substantially during this child's gestation and is still drinking and of childbearing age, she needs direction toward appropriate interventions to prevent subsequent adverse birth outcomes. She also needs support in rearing her child if she has custody. The child is considered at risk as well, based on the exposure history itself. Whether the child meets criteria for FAS, a related condition, or is found to be typically developing at the time of assessment, he or she needs appropriately stimulating home and preschool experiences and reassessments in the age period from kindergarten to second grade. As of 2000, few specific preschool programs have been specifically developed for children with FAS and related conditions (see Olson & Burgess, 1997). The need for more such programs is imperative for improving the quality of these children's lives.

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FETAL ALCOHOL SYNDROME (FAS) PRIMARY PREVENTION THROUGH FAS DIAGNOSIS: I. IDENTIFICATION OF HIGH-RISK BIRTH MOTHERS THROUGH THE DIAGNOSIS OF THEIR CHILDREN

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Abstract - A 5-year, FAS primary prevention study was conducted in Washington State to: 1) assess the feasibility of using a FAS Diagnostic and Prevention Clinic as a center for identifying and targeting primary prevention intervention to high-risk women (namely, women who had given birth to a child with FAS), 2) generate a comprehensive, lifetime profile of these women and 3) identify factors that have enhanced and/or hindered their ability to achieve abstinence. The results of this study are presented in two parts: Objective 1 is summarized in Part I below; Objectives 2 and 3 are summarized in Part II, published separately. This project demonstrated that a multidisciplinary FAS Diagnostic and Prevention Clinic (FAS DPN) could successfully attract and meet the diagnostic and treatment planning needs of patients presenting with prenatal alcohol exposure. One out of every three patients evaluated in the FAS DPN clinics was diagnosed with FAS or static encephalopathy/alcohol exposed. The birth mothers of one out of every three of these children diagnosed with FAS or static encephalopathy/alcohol exposed could be located and directly contacted. Half of the birth mothers directly contacted were still at risk for producing more children damaged by prenatal alcohol exposure. Thus, one out of every 18 children evaluated in the FAS DPN clinics had a birth mother who could be found and was at risk for producing more children damaged by prenatal alcohol exposure. Primary prevention programs targeted to this high-risk population could lead to measurable, cost-effective reductions in the incidence of FAS. Using this approach, the cost of raising a child with FAS would be roughly thirty times the cost of preventing FAS in the child. The benefit to the children, their mothers and society would be immeasurable.

INTRODUCTION

The fetal alcohol syndrome (FAS) is a permanent birth defect caused by heavy maternal use of alcohol during pregnancy. FAS is characterized by pre- and/or postnatal growth deficiency, central nervous system dysfunction (CNS) and a unique cluster of minor facial anomalies (Clarren and Smith, 1978). The presentation of each individual feature of the syndrome may be variably expressed with age. Estimates of the incidence of FAS range broadly from 1 to 3/1,000 live births documented in epidemiological studies to 1/10,000 live births documented in birth defect registries (Stratton et al., 1996; Abel, 1998). FAS is one of the leading known, non-genetic causes of mental retardation in the Western World (Abel and Sokol, 1987).

Although FAS is entirely preventable, the factors associated with maternal alcohol use during pregnancy are complex and resistant to change (Beckman, 1984a). Maximizing primary prevention efforts will require targeting limited prevention resources to women at highest risk for producing children damaged by prenatal alcohol exposure. Primary prevention refers to preventing the birth of children damaged by prenatal alcohol exposure. One such population is women who have already given birth to a child with FAS. FAS studies consistently report that women who have had one child with FAS, and who continue to drink, have progressively more severely affected children with subsequent pregnancies (May *et al*., 1983; Davis and Lipson, 1984; Abel, 1988).

It is axiomatic that the evolution of effective prevention and treatment programs for nearly any medical condition rests on the identification of sufficient numbers of patients so that interventions that are hypothesized to be effective can be appropriately evaluated. The identification of "patients" is made more difficult than usual in conditions like FAS when both the child and the parent should each be appropriately identified as "the patient." Unfortunately, the diagnosis in the child often is made after the child is no longer in the birth mother's custody and the diagnosticians have no direct access to the birth mother or her records. FAS is vastly misdiagnosed (Cordero *et al*., 1994; Floyd *et al*., 1994) and the birth mothers of children with FAS are rarely if ever identified and targeted for primary prevention intervention. Failure to identify and intervene with these two populations results in primary and secondary disabilities that come at high cost to the child, mother and society (Beckman, 1984; Abel and Sokol, 1987; Streissguth and Kanton, 1997).

The failure to medically diagnose FAS has complex antecedents. Based on our interactions with thousands of families attending our FAS diagnostic clinics and hundreds of medical professionals attending our diagnostic training sessions, in our opinion, these antecedents include three apparently commonly held beliefs. First, some physicians remain ignorant of the existence of FAS or the diagnostic approach to this syndrome, or any syndrome. Second, many physicians believe that intervention programs are equally effective for individuals with any etiologic form of mental retardation or attention deficit disorder and they fail to recognize the more complex and subtle brain damage in alcohol affected individuals. They also fail to recognize their role in helping to identify the birth mother for future prevention efforts through recognition of FAS in the child. Third, patients with FAS and their families often need help with foster or adoption support services, educational interventions, alcohol treatment, vocational rehabilitation, and/or the criminal justice system. Most physicians are not trained to lead intervention programs

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in these these arenas, nor are they likely to have well-established referral linkages to professionals in these other firleds. Further, many physicians may believe these issues are truly outside of the appropriate purview of pediatrics and 'healthcare'. Putting these false beliefs into practice sets up a self-defeating cycle. When physicians fail to perceive that a diagnosis of FAS will benefit the patient, the birth mother, the family, and society, FAS remains under-diagnosed. When individuals are not diagnosed, it is not possible to demonstrate the benefits of diagnosis to the child or the parent, nor can surveillance be done accurately enough to monitor the success of prevention efforts.

Although physician attitudes and training limit the availability and accuracy of FAS diagnostic services, we have found tremendous interest by families and professionals from social service, educational, and correctional facilities to obtain diagnostic confirmation of CNS dysfunction among individuals with prenatal alcohol exposure. They have shared with us that these diagnoses facilitate their intervention efforts with these individuals.

The ideas that stimulated this prevention project in 1992 arose from our experiences in the 1980s. Increasing knowledge of FAS in the medical literature and public media, and countless medical trainings on the subject did not seem to be changing medical practice in diagnosing FAS. Rather, we felt that a new team approach to diagnosis and treatment planning was needed in clinics dedicated to FAS issues if the beliefs described above were to be effectively challenged.

We believed that clinics dedicated specifically to FAS were the critical missing step in helping to solve this problem (Clarren and Astley, 1998). First, FAS clinics could provide a mechanism for demonstration of community interest in the diagnosis of FAS and an opportunity to determine which professionals or social/health care systems seek consultation and what issues or problems drive those referrals. The clinics could accurately make FAS diagnosis using appropriate and consistent assessments of physical, cognitive, and behavioral abnormalities. The clinics could recommend treatment programs and over time determine if these programs were available and, if available, effective. The clinics would stimulate ideas for novel treatment modalities and would generate enough patients and sufficient linkage to treatment venues that implementation and assessment could be done.

Second, clinics would become a critical resource in public awareness - FAS prevention programs. As the general public is made aware of FAS and related conditions and warned to avoid alcohol use in pregnancy, families who have children who might have FAS are also made aware of the disorder and they often become concerned. These families deserve to have appropriate diagnostic facilities nearby to answer their questions and provide appropriate diagnosis and treatment planning.

Third, clinics would be necessary to support active screening of high-risk populations like foster care or juvenile rehabilitation. Patients who screened positive would require a resource for final accurate diagnosis and counseling which could only be reliably met through dedicated clinics.

Fourth, the clinics could be a critical tool for primary prevention. Not all women alcoholics appear to be at equal risk for having children with FAS (Abel, 1995). Although women who have one affected child often have more, to date there is no anticipatory biologic or sociologic markers that distinguish the mothers of children with FAS from other women who drink in pregnancy and bear normal or nearly normal children. Treatment of women for alcoholism during pregnancy probably comes too late to prevent brain damage in affected fetuses even if the correct high-risk, alcoholic women are selected for therapy. While it would be ideal to identify and treat all alcoholic women prior to pregnancy, resources for such an effort are not available. However, each patient with FAS (as identified through a FAS diagnostic clinic) has a mother who has a proven potential to give birth to a child damaged by prenatal alcohol exposure. Focusing prevention efforts on this select and high-risk group of women could reduce the incidence of FAS births dramatically without unduly overburdening the current health care and alcohol treatment systems.

A Cooperative Agreement with the Centers for Disease Control and Prevention (CDC) from 1992 to 1997 allowed for the development of an FAS Clinic at the University of Washington that could demonstrate our conviction that misdiagnosis of FAS was occurring and could be corrected, and that the birth mothers of the patients could be found. Once found, the mothers could be interviewed to generate comprehensive lifetime profiles which, in turn, could be used to develop intervention programs targeted to meet their needs.

The specific objectives of this FAS diagnostic and prevention effort were to: (1) To assess the feasibility of using a FAS Diagnostic Clinic as a center for identifying and targeting primary prevention intervention to high-risk women. Specifically: (a) to establish an FAS Diagnostic Clinic; (b) determine the rate at which individuals with FAS could be identified; (c) determine the feasibility of identifying their birth mothers. (2) To generate a comprehensive, lifetime profile of their birth mothers as a first step in the development of a FAS primary prevention program targeted to meet their needs. Specifically, administer a personal, structured interview to the birth mothers of children diagnosed with FAS to document their: (a) sociodemographic profile; (b) social/health care utilization patterns; (c) adverse social experiences; (d) social support networks; (e) intelligence quotients (IQ); (f) mental health profiles; (g) reproductive and family planning histories; (h) alcohol use and treatment histories. (3) To identify factors that have enhanced and/or hindered the birth mothers' ability to achieve abstinence.

This report represents the first in a series of two reports that present the methods and outcomes of this FAS diagnostic and prevention project. This first report presents the complete methodology for the project and summarizes the project's success at identifying high-risk birth mothers through the diagnosis of their children (Objective I). The second report presents a lifetime profile of 80 birth mothers who gave birth to a child with FAS and identifies factors that enhanced and hindered their ability to achieve abstinence and/or practice effective family planning (Objectives II and III) (Astley *et al*., 2000).

METHODS

Establishment of the University of Washington FAS Diagnostic and Prevention (FAS DPN) Clinic

The first step in meeting the objectives above was to establish a multidisciplinary FAS diagnostic and prevention clinic at the University of Washington. The ultimate purpose of the clinic was to identify and target primary prevention services to women who had given birth to a child with FAS. To achieve this goal, the clinic had to effectively attract patients with FAS. After 25 years of experience making diagnoses in a variety of clinical settings, it was clear that this could best be accomplished by establishing a multidisciplinary clinic prepared to meet not only the diagnostic needs, but also the social service, educational and behavior management needs of the patients and their caregivers. This multidisciplinary approach to FAS diagnosis and prevention is described in detail in separate publications (Clarren and Astley, 1997; Clarren et. al., 2000).

Sources of Patients

Two sources of patients with FAS were used to address Objectives 1 through 3: 1) patients diagnosed through the CDC-sponsored University of Washington FAS Clinic and 2) patients diagnosed through other University of Washington or Children's Hospital and Regional Medical Center neurodevelopmental and genetics clinics. The CDC-sponsored FAS Clinic opened in 1993. Patients were identified through this clinic prospectively at the time of their diagnostic evaluation. The University of Washington and Children's Hospital clinics opened in the 1970s and were operational throughout this study. Patients were identified through these clinics both retrospectively and prospectively through research and medical records. The diagnosis of FAS did not begin with the CDC-sponsored University of Washington FAS Clinic in 1993. The diagnosis of FAS has been actively made in these clinical systems since the early 1970s when David Smith, M.D. and his colleagues identified the first cases in the United States (Jones and Smith, 1973). Dr. Clarren has been actively making the FAS diagnosis, using the same criteria, since entering practice in 1978 (Jones and Smith, 1973; Clarren and Smith, 1978; Rossett, 1980; Sokol and Clarren, 1989).

To assess the feasibility of using a FAS Clinic as a center for identifying and targeting primary prevention services to high-risk women (Objective I), patients diagnosed with FAS prospectively in the CDC-sponsored University of Washington FAS Clinic were used. This single clinic expanded into the Washington State FAS Diagnostic and Prevention Network (FAS DPN) of seven clinics in the third year of the study to meet the ever-increasing demand for diagnosis. This expansion is described in more detail below.

To generate a lifetime profile of birth mothers of children with FAS and to identify factors that enhanced and hindered their ability to achieve abstinence (Objectives II and III), patients from both sources were used. The addition of this second source of patients served to increase the total number of birth mothers enrolled in the study and served to increase the maternal follow-up period of observation subsequent to the birth of the index child with FAS. The longer the period of follow-up on the birth mothers, the more meaningful the lifetime profiles and identification of factors that enhanced and hindered abstinence and family planning.

Diagnostic Criteria

The diagnoses of FAS and 'static encephalopathy/alcohol exposed' were made using the clinical gestalt guidelines published by Sokol and Clarren (1989) and the 4-Digit Diagnostic Code created by Astley and Clarren (1997, 1999, 2000). The diagnosis of FAS was accepted when Dr. Clarren made that diagnosis or when the diagnosis was made by another clinician and Dr. Clarren had reviewed the data and concurred.

In the last year of this project, a new, comprehensive, case-defined method for diagnosing FAS called the 4-Digit Diagnostic Code was established by the University of Washington FAS Clinic under a separate contract (Astley and Clarren, 1997, 1999, 2000). This new method was created in response to both the Institute of Medicine's recommendations that a more reliable and valid set of diagnostic definitions be adopted (Stratton *et. al*., 1996) and our Washington State Senate's mandate that we assure diagnostic reproducibility among all Washington State FAS DPN clinics. This new diagnostic system documents the magnitude of expression of the four key components of the syndrome: 1) growth impairment, 2) the FAS facial phenotype, 3) evidence of brain damage and 4) prenatal alcohol exposure, on separate 4-point Likert scales (Astley and Clarren, 2000). Likert Rank 1 represents normal. Likert Rank 4 represents the most severe expression of the feature. Generally speaking, a diagnosis of FAS requires ranks of 3 or 4 in all four categories. This new system of diagnosis was implemented in the U.W. FAS Clinic during the last six months of this project.

Maternal Study Population

The target population for this prevention project was initially birth mothers of children who received a gestalt diagnosis of FAS. Implementation of the 4-Digit Code method of diagnosis in the last six months of the project allowed us to expand the maternal target population to all women who gave birth to infants with documented brain dysfunction and prenatal alcohol exposure, not just the subset who gave birth to children with FAS. One of the many benefits of the 4-Digit Code is that is clearly differentiates patients with organic brain damage and prenatal alcohol exposure from the much larger and heterogeneous group previously labeled through the gestalt method of diagnosis as possible fetal alcohol effects (PFAE). With the implementation of the 4-Digit Code, the diagnostic criteria were expanded to include all children who received a diagnosis of static encephalopathy (4-Digit brain Likert ranks of 3 or 4) and confirmed prenatal alcohol exposure (4-Digit alcohol Likert ranks of 3 or 4) with or without the FAS facial phenotype or growth deficiency. Children who also presented with the FAS facial phenotype and growth deficiency were the subset of children with static encephalopathy who met the criteria for a diagnosis of FAS. To obtain a 4-Digit brain rank of 3 or 4, a patient must present with microcephaly, a seizure disorder, an abnormal CT or MRI, a full scale IQ < 60, or performance of greater than two standard deviations below the norm across three or more of the following domains in a psychometric assessment battery (intelligence, achievement,

adaptation, neuropsychology and language). This expanded target population reflects a very high-risk group of women (Abel, 1988), who are not only uniquely and conveniently identifiable through a FAS Diagnostic Clinic, but ideally targeted for primary prevention intervention. Women who were eligible to enroll in this study met the following criteria:(1) they gave birth to at least one child with a medical diagnosis of FAS or static encephalopathy/alcohol exposed rendered or confirmed by SKC following the clinical guidelines of Sokol and Clarren (1989) or Astley and Clarren (1997, 1999, 2000); (2) they were of any age or race; (3) they were a resident of Washington State at the time of study enrollment; (4) they consented to participate in the study.

Identification, Location and Enrollment of Birth Mothers

This study was reviewed and approved by the University of Washington Human Subjects Review Board. The process for identifying individuals with FAS and identifying, locating and inviting their birth mothers to enroll in this study was done in compliance with medical and research policy for protecting patient confidentiality.

Birth mother identification, location and enrollment was conducted by a social worker over a 36-month period. Identification and location of the birth mothers was accomplished either through direct contact with them when they accompanied their child to the diagnostic examination, or through letters or phone calls of invitation delivered by family, friends and social/medical providers when they did not attend their child's diagnostic examination. Public records such as phone directories, driver's license bureaus, birth and death certificates and Department of Correction registries were used when necessary to identify and locate the women.

Birth mothers who attended their child's diagnostic evaluation in any clinic in which SKC was the diagnosing physician were invited to enroll in the study by SKC at the time of the diagnostic evaluation or through receipt of a letter from SKC. Women who did not attend their child's diagnostic evaluation, but whose names were documented in their child's diagnostic record received a letter of invitation from SKC as the child's treating physician. Women whose names were not known by the FAS DPN clinic were sent letters of invitation from SKC through a family member, friend or medical/social service professional that did know the women. This allowed the birth mother to be invited to learn more about the study without revealing her name or location to the FAS DPN study staff. If she was interested in participating, the letter of invitation included a stamped, response postcard, addressed to the FAS DPN, allowing her to contact us or give us permission to contact her.

Every effort was made to facilitate the woman's participation in the study. Offering child-care, transportation, flexible scheduling, and mobile interviewing were key in enrolling women. Additionally, as long as the parameters of the interview were maintained (private room, no interruptions), women were encouraged to choose the setting of the interview. Interviews took place in a variety of settings – public health centers, hospitals, community centers, treatment centers, libraries, correctional facilities, and homes – and at a time convenient to the women.

Maternal Interview

A four-hour structured personal interview was developed to generate a lifetime, comprehensive profile of each birth mother's sociodemographics, reproductive and family planning history, social and health care utilization patterns, adverse social experiences, social support network, alcohol use and treatment history, psychosocial profile and intelligence quotient. The interview included 2,044 questions. The questions focused on three time periods in the women's lives: (1) at the birth of the index child with FAS; (2) at the time of the interview; (3) over their lifetime. The interview included the following standardized (indicated by *) and non-standardized instruments: (1) Sociodemographic and Lifetime Social/Health Care Utilization Questionnaire; (2) Reproductive and Family Planning History Questionnaire; (3) Social Support Questionnaire (Short Version)* (Sarason *et al*.,1987); (4) Quick Diagnostic Interview Schedule III R* (Bucholz *et al*., 1996); (5) Shipley-Hartford Institute of Living Scale* (Shipley, 1967); (6) Alcohol Use and Treatment History Questionnaire.

The Sociodemographic and Lifetime Social/Health Care Utilization Questionnaire was constructed to document lifetime education, employment, physical and social home environment, social/health care utilization patterns, and adverse social experiences. The Reproductive and Family Planning History Questionnaire was constructed to document: 1) for all conceptions (mother's age, birth outcome, form of birth control used, planfulness of conception and alcohol exposure) and for all types of birth control available (age when used, ever failed, currently using, if stopped using-why and if available at no cost-would she use it now). The Alcohol Use and Treatment History Questionnaire documented lifetime drug and alcohol use and all concerted efforts to reduce alcohol use. The women were first asked to list all concerted efforts to reduce intake by date and then to provide the following details on three specific efforts; the most successful, the least successful and the effort closet to the birth of the index child with FAS. For each of these three efforts they were asked to report: (1) their level of alcohol use; (2) reasons for attempting to reduce their intake; (3) pertinent sociodemographics; (4) alcohol treatment program parameters; (5) family support; (6) need and access to social/educational/medical services during their treatment; (7) their perceived level of success or failure in reducing their alcohol use; (8) reasons they attributed to their success or failure. This questionnaire was designed to address many of the issues raised by Beckman and Braiker on the treatment needs of women alcoholics and the structural, personal and environmental barriers to treatment (Beckman, 1980, 1984, 1984a; Beckman and Amaro, 1984; Braiker, 1984). It also incorporated questions that addressed key findings of a 1993 Seattle-based survey of chemical dependency treatment programs serving women (Seattle-King County Task Force for Chemically Dependent Women, 1993). The Short Social Support Questionnaire is a standardized instrument of twelve questions (Sarason *et al*., 1987). The respondent is asked to list the number of people they can depend on to provide them with help or support (e.g., "Whom can you count on to console you when you are very upset?") and to rank their level of satisfaction with the support they receive on a six-point scale. The Shipley-Hartford Institute of Living Scale is a standardized instrument of 60 self-administered questions used to derive an

estimate of the WAIS-R full-scale intelligence quotient (I.Q.) (Shipley, 1967). The National Institute of Mental Health Quick DIS-III-R is a computerized interview used to diagnose lifetime psychiatric disorders in accordance with DSM-III-R criteria for positive symptoms (Busholz *et al*., 1996). The following components were administered by the trained interviewer: demographics, panic disorder, generalized anxiety disorder, agoraphobia, social phobia, simple phobia, post-traumatic stress disorder, major depressive episode, manic episode/bipolar disorder, schizophrenia/schizophreniform, anorexia, bulimia, alcohol disorder and antisocial personality. The computer program reports the diagnostic outcome (+/-) for each disorder and the age at onset of symptoms.

At the completion of the 4-hour study interview, the women received $75 and referrals to services specific to their needs. The interview was constructed through a collaborative effort between medical and social service providers at the University of Washington, Washington State Department of Public Health, Seattle/King County Department of Public Health and the CDC. The interview was administered by a single registered nurse with a master's degree in addictions nursing.

Analysis

t-tests, Mann-Whitney Rank Sum tests and chi-square (or Fisher Exact) tests were used to compare outcomes between two independent groups when the outcomes were measured on continuous, ordinal or nominal scales respectively.

RESULTS

Establishment of the FAS Diagnostic Clinic

The UW FAS Clinic opened in January 1993. The format and function of the clinic are described in full in Clarren and Astley (1997) and Clarren et. al (2000). Briefly, the clinic at the University of Washington was and continues to be held one day per week and sees two to four patients and their caregivers per day. A multidisciplinary team that includes a pediatrician (SKC), educational and clinical psychologists, an occupational therapist, a speech language pathologist, maternal advocate and a family advocate staff the clinic. Applications for appointments are taken over a telephone hotline. Patients seek their own appointment or are seen on referral. Referrals come primarily from social service agencies, educational facilities, the criminal justice system and rarely from physicians or other health care providers. All persons who call are sent a New Patient Information Form to complete. The form documents the patient's physical and developmental history, gestational exposures and caregiver's concerns. The completed and returned forms are reviewed and prioritized based on the urgency of the request. Caregivers are asked to bring copies of previous school, medical and psychological evaluations to clinic on the day of their appointment. The caregivers are interviewed jointly by the pediatrician and psychologist, and the patient is examined to determine if he/she has the physical features of FAS. The patient also receives brief language, neurologic and psychometric assessments. After the interview and clinical examination, the clinic team completes the FAS Diagnostic Evaluation Form (Astley and Clarren, 1997) derives a 4-Digit diagnosis and generates a referral plan for treatment and services for the patient, their family and the birth mother if appropriate. The caregivers then meet with the Clinic team to discuss the diagnosis and referrals. The caregivers receive a complete medical summary within three weeks after their clinic visit.

The clinic was so successful in meeting the diagnostic needs of families, as demonstrated by the patient satisfaction surveys presented above, that it was unable to deal with the very large demand for services. Working first with the Western Washington Chapter of the March of Dimes Birth Defects Foundation and then with the Washington State Legislature, a law was passed in 1995 which directed us to develop community-based clinics like the one at the University throughout the state. This was the beginning of the Washington State FAS Diagnostic and Prevention Network (FAS DPN). The FAS DPN is a consortium of six community-based clinics located at major population centers around Washington State led by the core diagnostic and training clinic at the University of Washington. While this was not a specific objective of this CDC cooperative agreement, ensuring the continuation of this project through other forms of support beyond the 5-year Cooperative Agreement was certainly a positive outcome. It also led to an increased capacity to identify birth mothers in the last two years of this study.

The mission of the FAS DPN is primary and secondary prevention of FAS through clinical screening, diagnosis, research and training. To accomplish this mission, comprehensive, case-defined methods for FAS screening (Astley and Clarren, 1996) and diagnosis (Astley and Clarren, 1997, 1999, 2000; Astley *et al*., 1999) were developed and implemented. A clinical training program was established at the University of Washington core site to provide FAS training to local community professionals and multidisciplinary clinical teams worldwide. The screening, diagnostic and training tools were all developed from the FAS DPN clinical database. This database also serves as a confidential registry of over 1,200 consistently diagnosed patients eligible to enroll in ongoing prevention/intervention research. The FAS DPN clinics are unique from other genetic and neurodevelopmental programs that typically provide services to these children in three fundamental ways: 1) The FAS DPN clinics all follow the same comprehensive, case-defined method for diagnosis (Astley and Clarren, 1997, 1999, 2000), 2) the clinics provide a multidisciplinary approach to diagnosis and treatment planning (Clarren and Astley, 1997; Clarren et. al., 2000) and 3) the clinics focus their intervention efforts on both the child and the birth mother (diagnosis and treatment planning for the child with primary prevention intervention for the child's birth mother). The patient satisfaction survey presented to all patients seen in the FAS DPN revealed that 87% of patients felt they had received services they were unable to obtain anywhere else. Ninety-nine percent reported they would recommend the clinic to families in similar need. The Network is currently funded through multiple sources including in-kind support, fee for service, and specific grants and contracts to provide targeted services within the community.

Proportion of Patients Receiving a FAS Diagnosis in the FAS DPN Clinics

The FAS DPN clinics received 3,002 requests for diagnostic evaluations in its first five years of operation (1993

through 1997). Operating at capacity, the clinic conducted 811 diagnostic evaluations.

Gestalt Method. The first 454 patients evaluated in the FAS Clinic were diagnosed using the gestalt method. Of the 454 patients, 110 (24.2%) received a gestalt diagnosis of FAS or atypical FAS (AFAS) and 344 (75.8%) received a gestalt diagnosis of PFAE. AFAS is FAS without the growth deficiency. Using the gestalt method, one out of every four patients received a diagnosis of FAS/AFAS.

4-Digit Code Method: Patients 455 through 811 were diagnosed using the 4-Digit Diagnostic Code method. All 454 patients diagnosed prior to implementation of the new diagnostic method had their gestalt diagnostic outcomes converted over to the new, more stringently case-defined 4-Digit Code. Thus, of all 811 patients evaluated at the FAS DPN, 39 (4.8 %) received a 4-Digit diagnosis of FAS/AFAS (Diagnostic Categories A-C) and 559 (68.9 %) received a 4-Digit diagnosis (Diagnostic Categories E-I) comparable to the gestalt diagnosis of PFAE. Using the 4-Digit Code method, one out of every 21 patients evaluated in the FAS DPN Clinics received a 4-Digit diagnosis of FAS/AFAS. A lower proportion of patients were diagnosed with FAS using the 4-Digit Code relative to the gestalt method because the 4-Digit Diagnostic system demands more stringent adherence to the diagnostic criteria of FAS through the use of specific case definitions (Astley and Clarren, 2000).

Impact of the 4-Digit Code on Identifying High-Risk Mothers

In contrast to the maternal population initially targeted in this study through their child's gestalt diagnosis of FAS, the 4-Digit diagnostic system allowed a much broader and more appropriate maternal population to be accurately identified and targeted for primary prevention. In other words, rather than target the birth mothers of just the children with FAS/AFAS, the birth mothers of all children receiving a 4-Digit diagnosis ending in 33, 34, 43, or 44 could and should be targeted. These codes reflect strong evidence of organic brain damage (static encephalopathy) and a confirmed history of maternal alcohol exposure. Of the 811 patients evaluated at the FAS DPN, 238 (29 %) received a diagnosis of static encephalopathy/alcohol exposed. Thirty-nine of these 238 patients (16.4%) also presented with growth deficiency and the FAS facial phenotype and thus received a 4-Digit diagnosis of FAS/AFAS. Thus one out of every three patients evaluated in the FAS DPN Clinics received a 4-Digit diagnosis of static encephalopathy, alcohol exposed. This is the maternal population currently being targeted for primary prevention intervention in the FAS DPN clinics.

Identification and Enrollment of Birth Mothers

A total of 257 women who had given birth to one or more children with a gestalt diagnosis of FAS (Sokol and Clarren, 1989) or a 4-Digit diagnosis of FAS or static encephalopathy (Astley and Clarren, 1997, 1999, 2000) were identified as potentially eligible to enroll in this study (Table 1). One hundred and forty-seven (57%) were identified prospectively from the FAS DPN clinics and 110 (43%) were identified both retrospectively and prospectively from other clinics. Of the 257 mothers, 92 were confirmed to be eligible to enroll in this study, 58 were confirmed to be ineligible and the eligibility of the remaining 107 remained unknown. Of the 92 mothers confirmed to be eligible, 80 (87%) were enrolled and interviewed. Of the 58 women who were deemed ineligible, 31 no longer lived in Washington State and 27 were deceased. Of the 107 women whose eligibility status could not be determined, 97 were identified by name, but none of them could be located.

Key challenges to locating the birth mothers included: 1) 80% of the children were no longer in the custody of their birth mothers at the time of the child's diagnosis, and 2) medical confidentiality limited the exchange of patient/birth mother information between our study staff and outside agencies who could be instrumental in assisting us. It required, on average, 6.7 (range = 1 to 36) attempts to contact each of the 80 women over an average of 3.8 months (range = 0 to 36 months) per woman to identify, locate and enroll them into the study. We found that public health and social service providers were very willing to help locate the women when they could. Most often, they would telephone or forward letters of invitation from us to the eligible women.

Success at identifying, locating and enrolling women was comparable between the two clinical sources (Table 1). The majority of the children diagnosed with static encephalopathy/alcohol exposed came from the FAS DPN clinics because the majority of children diagnosed in the other clinics were diagnosed before the 4-Digit Code was created and only children seen by SKC in the other clinics were diagnosed using the 4-Digit Code. The patient population at the FAS DPN also had a slightly higher proportion of Caucasians than the patient populations identified through the other clinics.

Representativeness of the Maternal and Patient Study Populations

The maternal population that the FAS DPN clinics will target for primary prevention efforts are the birth mothers of children with FAS and static encephalopathy who can be identified and located with reasonable effort and live within Washington State where they are eligible to receive social and health care services. This target population is defined by the eligibility criteria presented above for this study. Eighty (87%) of the 92 women confirmed to be eligible to enroll in this study were enrolled and interviewed (Table 1). Of the 12 eligible women who did not enroll, six were identified by name and location, but could not be reached directly to invite into the study. Of the six women who were contacted, but declined to interview, five of them had given birth to the index child with FAS over 17 years ago and one had given birth to the index child with FAS only four months ago. Two of these six patients had been diagnosed over ten years ago. Four of these women said they were too old or unhealthy to participate, one said that she was too busy, and one did not provide a reason. Based on the percent of eligible women interviewed (87%), this study population should be reasonably representative of the target population. Although the primary objective of this

Table 1. Summary of maternal identification, location and enrollment stratified by whether the child was identified prospectively in a FAS Diagnostic & Prevention Network clinic (FAS DPN) or retrospectively/prospectively in another clinic.

Characteristic	Source of Patient with FAS or Static Encephalopathy: Prospective FAS DPN Clinics n	(%)	Retrospective/Prospective Other Clinics n	(%)	Total n	(%)
Birth mothers of children diagnosed with FAS or static encephalopathy	147		110		257	
Maternal interview status						
Interviews completed	46	(31.3)	34	(30.9)	80	(31.1)
Interview not completed	101	(68.7)	76	(69.1)	177	(68.9)
Reasons interview not completed:	(Among 101)		(Among 76)		(Among 177)	
Not eligible	32	(31.7)	26	(34.2)	58	(32.8)
Did not live in WA State	20		11		31	
Deceased	12		15		27	
Eligibility Unknown	63	(62.4)	44	(57.9)	107	(60.5)
Identified but not located	55		42		97	
Not identified or located	8		2		10	
Eligible, but:	6	(5.9)	6	(7.9)	12	(6.7)
No direct contact achieved	5		1		6	
Declined to interview	1		5		6	
Identification and location success	(Among 147)		(Among 110)		(Among 257)	
Identified by name	139	(94.6)	108	(98.2)	247	(96.1)
Identified by name and located	84	(57.1)	66	(60.0)	150	(58.4)
Identified by name but not located	55	(37.4)	42	(38.2)	97	(37.3)
Not identified by name or located	8	(5.5)	2	(1.8)	10	(3.9)
Child's diagnosis -- method of diagnosis **						
FAS: Gestalt or 4-Digit	119	(80.9)	106	(97.2)	225	(87.9)
Static encephalopathy: 4-Digit	28	(19.1)	3	(2.8)	31	(12.1)
Child's race *						
Caucasian 93	(67.4)	51	(56.0)	144	(62.9)	
African American	11	(8.0)	8	(8.8)	19	(8.3)
Native Amer., Alaskan or Canadian	25	(18.1)	30	(33.0)	55	(24.0)
All others	9	(6.5)	2	(2.2)	11	(4.8)

* P < 0.05; ** P < 0.01.

prevention project was to demonstrate the feasibility of targeting primary prevention services to birth mothers identified prospectively through the FAS DPN clinics; women identified from other diagnostic clinics were also enrolled to increase the sample size and duration of follow-up. Inclusion of women from outside the FAS DPN did not appear to impact the overall maternal profile. The sociodemographic profiles of the two clinical populations were very comparable. The 46 mother/child pairs identified through the FAS DPN and the 34 mother/child pairs identified through the other clinics did not differ significantly in maternal race, maternal education level, maternal age at the time of the child's birth, maternal age at the child's diagnosis, maternal age at the time of the interview; child's race, child's gender or the child's age at the time of the maternal interview. The mean age of the patients diagnosed in the FAS DPN clinics was older than the patients diagnosed in the other clinics (9.4 ± 6.2 compared to 5.7 ± 4.8; $t = 2.8$, $p = 0.006$) because the FAS DPN clinics see both children and adults. The other clinics were all pediatric clinics. Patients identified through the other clinics had been diagnosed longer ago relative to the patients identified through the FAS DPN (4.8 ± 4.2 years compared to 1.4 ± 1.1 years; $t = 4.4$, $p = 0.000$), which was expected since the other clinics opened in the 1970s. The magnitude of these two contrasts is not likely to have a meaningful impact on the overall profile of the maternal target population.

One additional contrast that will be of interest to some is a comparison of the 80 women who were enrolled versus the remaining 177 who were identified as having given birth to a child with FAS or static encephalopathy, but were not enrolled. The following sociodemographic characteristics were comparable between the two groups: the child's diagnosis, mother's race, mother's age at the child's birth, mother's age at the child's diagnosis and mother's age at the time she was identified as potentially eligible to be enrolled in the study. A complete sociodemographic profile of the 80 women enrolled in the study can be found in Table 1 in Part II of this series (Astley *et al*., 2000). The children of the mothers who were not enrolled were on average three years older at the time of their diagnosis (10 ± 9 compared to 8 ± 6; $t = 2.6$, $p = 0.01$), were more likely to be female (45% compared to 31%; chi-square = 4.2; $P = 0.04$) and were diagnosed 1 year earlier (4.4 ± 4.3 compared to 3.5 ± 3.0; $t = 3.6$, $P = 0.000$) than children of the women enrolled. Again, it would appear that the maternal

Table 2. Selected characteristics of the 80 children whose birth mothers were interviewed.

Characteristic	mean	(S.D.)	min. - max.	n	(valid %)
Age (years) at time of diagnosis					
0.0 to 5.9				37	(46.3)
6.0 to 10.9				18	(22.5)
11.0 to 15.9				20	(25.0)
16.0 +				5	(6.2)
Mean	7.8	(5.9)	0.1 - 24.2	80	
Age (years) at time of interview	10.5	(6.2)	0.6 - 25.5	80	
Gender, male:female (% female)				55:25	(31.3)
Race					
Caucasian				51	(63.8)
African American				8	(10.0)
Native American, Alaskan or Canadian				19	(23.7)
Hispanic				2	(2.5)
Primary caregiver at the time of the child's diagnosis					
Birth mother with or without birth father				38	(47.5)
Birth father only				3	(3.7)
Other family members				10	(12.5)
Adoptive/foster parent				24	(30.0)
Other (group home, therapeutic center, juvenile detention)				5	(6.3)
Clinical source for patient identification					
FAS DPN clinics (1993 to 1997)				46	(57.5)
Other clinics				34	(23.5)
Diagnosed by author (SKC)				72	(90.0)
Child's Diagnosis for Maternal Enrollment: Method of Diagnosis					
FAS: Gestalt or 4-Digit Code				70	(87.5)
Static encephalopathy: 4-Digit Code				10	(12.5)
Child's Diagnosis transformed into 4-Digit Diagnostic Code					
FAS/AFAS (Diagnostic Categories A, B, or C)				23	(30.3)
Static Encephalopathy, alcohol exposed					
With or without sentinel physical findings				32	(42.1)
Neurobehavioral Disorder, alcohol exposed					
With or without sentinel physical findings				21	(27.6)
Sufficient data not available to generate Code				4	(---)

population enrolled is reasonably representative of the population of all mothers identified through the diagnosis of their children.

*Profile of the 80 Children whose Mothers were Enrolled***.**

A profile of the 80 children whose mothers were enrolled in the study is presented in Table 2. They were predominantly Caucasian, 7.8 years of age at the time of their diagnosis with over half no longer living with their birth mother at the time of the diagnosis. The racial distribution was comparable to the racial distribution in WA State with the exception of a slight over representation of Native Americans. Eighty-nine percent had a gestalt or 4-Digit diagnosis of FAS, the remaining 11% had a 4-Digit diagnosis of static encephalopathy/alcohol exposed without the full FAS facial phenotype.

DISCUSSION

This project demonstrated that the multidisciplinary FAS DPN of clinics could successfully attract and meet the diagnostic and treatment planning needs of patients presenting with prenatal alcohol exposure. The clinical database generated from this patient population allowed for the development of screening and diagnostic tools that, in turn, allowed the clinic and its diagnostic method to be replicated statewide and nationally. The FAS DPN was successful at attracting a patient population at high risk for organic brain damage and prenatal alcohol exposure. Using the original gestalt method of diagnosis, one out of every four patients evaluated received a diagnosis of FAS. Using the 4-Digit Diagnostic Code method of diagnosis that demands more stringent adherence to strict diagnostic criteria, 238 (29 %) of the 811 patients evaluated through the FAS DPN Clinics received a diagnosis of static encephalopathy/alcohol exposed. Thirty-nine of these 238 patients (16.4%) also presented with growth deficiency and the FAS facial phenotype and thus received a 4-digit diagnosis of FAS/AFAS. Thus one out of every three patients evaluated in the FAS DPN clinics received a 4-Digit diagnosis of static encephalopathy, alcohol exposed. The birth mothers of these children with documented organic brain damage and prenatal alcohol exposure represent the FAS

DPN's current target population for primary prevention intervention. While only 20 % of the patients evaluated in the FAS DPN clinics are accompanied by their birth mother, the clinic was able to identify 95% and locate 57% of them. Forty-six percent of the 80 women interviewed in this study were still at risk for producing alcohol-damaged children at the time the index child received a diagnosis of FAS or static encephalopathy. They were at risk because they were still fertile and either actively drinking or at risk of drinking. Thirty-five had given birth to 61 additional children in the years following the index child's diagnosis. Seventy-five percent of the 61 children were exposed to alcohol in utero. Thus, based on what we have learned from this study: 1) that these women are at high risk for producing more children damaged by alcohol exposure, 2) that they, themselves, are often facing serious adverse social, mental and physical health issues, and 3) that some are often just a few phone calls away, one could argue that it would be unethical to ignore their existence and ignore the opportunity to provide them with advocacy support and primary prevention intervention (Astley *et al*., 2000).

Current Status of the Washington State FAS DPN Primary Prevention Program

The Washington State FAS DPN meets monthly with pertinent state agencies and programs (Department of Health, Department of Social and Health Services, Department of Corrections, Office of Public Instruction, Medical Assistance Administration, Family Advocacy, Western Washington March of Dimes and the University of Washington Fetal Alcohol and Drug Unit) to facilitate efficient and effective provision of FAS screening, diagnostic, prevention and educational services statewide. The FAS DPN is currently working with the State to facilitate referral of high-risk women identified through the FAS DPN to appropriate primary prevention intervention services. One state-supported service that provides very high-risk mother/infant pairs with home-based paraprofessional advocacy from birth to three years of age is the Washington State Parent-Child Assistance Program (P-CAP) directed by Therese Grant, Ph.D., at the University of Washington. P-CAP has proven to be highly effective and efficient at leading women into sobriety and effective family planning (Grant *et al*., 1999, Ernst *et al*., 1999). When the FAS DPN of clinics first opened in 1995, P-CAP had only one site in Seattle, Washington and enrolled only women who were in their last trimester of pregnancy with chronic alcohol and/or drug use during pregnancy. In 1999, the Washington State legislature supported the expansion of P-CAP into four of the six major metropolitan areas of Washington State where FAS DPN clinics exist and expanded the enrollment criteria to include birth mothers of children diagnosed with FAS or static encephalopathy through the FAS DPN clinics. While not all birthmothers targeted for primary prevention through the FAS DPN clinics need the intense services of P-CAP, those that do are well held.

Rate of Identification of Children and Mothers and Cost of FAS Prevention

Based on the results of this study, one out of every three patients evaluated in the FAS DPN clinics is diagnosed with FAS or static encephalopathy/alcohol exposed. The birth mothers of one out of every three of these children diagnosed with FAS or static encephalopathy/alcohol exposed can be directly contacted. Half of the birth mothers directly contacted will still be at risk for producing more children damaged by prenatal alcohol exposure. Thus one out of every 18 children evaluated in the FAS DPN clinics has a birth mother who can be found and is at risk for producing more children damaged by prenatal alcohol exposure.

Providing diagnostic and intervention services to both mother and child through a FAS Diagnostic Clinic not only benefits the mother and child, but has the potential of being a very cost effective approach to FAS primary prevention. The cost to society to raise a child with FAS is estimated to be $1,000,000 (Abel and Sokol, 1987). A diagnostic evaluation for a child through a FAS DPN clinic costs approximately $1,200. Providing effective intervention to the highest risk birth mothers through the Parent-Child Assistance Program costs $3,800 per year per woman for three years (Grant *et al*., 1999). If, on average, 18 children must be diagnosed to identify and intervene with one high-risk mother, the approximate cost to find and provide effective intervention services to the birth mother would be $33,000 ($22,600 to diagnose 18 children and $11,400 to provide three years of advocacy services to the mother through the P-CAP program). Thus, the cost of raising a child with FAS would be roughly thirty times the cost of preventing FAS in the child. The benefit to the mothers, their children and society would be immeasurable.

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FETAL ALCOHOL SYNDROME (FAS) PRIMARY PREVENTION THROUGH FAS DIAGNOSIS: II. A COMPREHENSIVE PROFILE OF 80 BIRTH MOTHERS OF CHILDREN WITH FAS.

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Abstract -- A 5-year, FAS primary prevention study was conducted in Washington State to: 1) assess the feasibility of using a FAS Diagnostic and Prevention Clinic as a center for identifying and targeting primary prevention intervention to high-risk women, 2) generate a comprehensive, lifetime profile of these women and 3) identify factors that have enhanced and/or hindered their ability to achieve abstinence. The results of this study are presented in two parts. Objective 1 is summarized in Part I and is published separately. Objectives 2 and 3 are summarized in Part II below. Comprehensive interviews were conducted with 80 women, who had given birth to a child diagnosed with FAS, to document their sociodemographics, reproductive and family planning history, social and health care utilization patterns, adverse social experiences, social support network, alcohol use and treatment history, mental health and intelligence quotient. This high-risk population of women was diverse in racial, educational and economic background, was often victims of abuse and was challenged by mental health issues. Despite their rather harsh psychosocial profile, many demonstrated the ability to overcome their alcohol dependence over time. The women who had achieved abstinence had significantly higher I.Q.s, higher household incomes, larger more satisfactory social support networks, were more likely to report a religious affiliation and were more likely to be receiving mental health treatment for their mental health disorders relative to the women who had not achieved abstinence. The rate of unintended pregnancies and alcohol-exposed pregnancies was substantial. Key barriers to achieving effective family planning were maternal alcohol and drug use, lack of access to birth control and lack of support by their partner to use birth control. A FAS Diagnostic and Prevention Clinic can be used to identify women at high risk for producing children damaged by prenatal alcohol exposure. Primary prevention programs targeted to this population could lead to measurable reductions in the incidence of FAS.

INTRODUCTION

The fetal alcohol syndrome (FAS) is a permanent birth defect caused by maternal use of alcohol during pregnancy. FAS is characterized by pre- and/or postnatal growth deficiency, central nervous system dysfunction (CNS) and a unique cluster of minor facial anomalies (Clarren and Smith, 1978). Prevention of FAS requires targeting primary prevention interventions to women at highest risk to produce children damaged by prenatal alcohol exposure. FAS studies consistently report that women who have had one child with FAS, and who continue to drink, have progressively more severely affected children with subsequent pregnancies (May *et al*., 1983; Davis and Lipson, 1984; Abel, 1988).

Although women who have one affected child often have more, to date there is no anticipatory biologic or sociologic markers that distinguish the mothers of children with FAS from other women who drink in pregnancy and bear normal or nearly normal children. Treatment of women for alcoholism during pregnancy probably comes too late to prevent brain damage in affected fetuses even if the correct high-risk, alcoholic women are selected for therapy. While it would be ideal to identify and treat all alcoholic women prior to pregnancy, resources for such an effort are not available. However, each patient with FAS (as identified through a FAS diagnostic clinic) has a mother who has a proven ability to give birth to a child damaged by prenatal alcohol exposure. Focusing prevention efforts on this select and high-risk group of women could reduce the incidence of FAS births dramatically without overburdening the current health care and alcohol treatment system (Clarren and Astley, 1998).

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A Cooperative Agreement with the Centers for Disease Control and Prevention (CDC) from 1992 to 1997 allowed for the development of a FAS Diagnostic Clinic at the University of Washington to: (1) assess the feasibility of using a FAS Diagnostic Clinic as a center for identifying and targeting primary prevention intervention to high-risk women; (2) generate a comprehensive, lifetime profile of their birth mothers as a first step in the development of a FAS Primary Prevention Program targeted to meet their needs; (3) identify factors that have enhanced and/or hindered the birth mothers' ability to achieve abstinence.

The methods and outcomes of this FAS diagnostic and prevention project are presented in two parts. The first report presents the objectives and methodology for the entire project and summarizes the project's success at identifying high-risk birth mothers through the diagnosis of their children (Objective I). This second report presents a lifetime profile of 80 women who gave birth to a child with FAS and identifies factors that enhanced and hindered their ability to achieve abstinence and/or practice effective family planning (Objectives II and III).

METHODS

A detailed presentation of the methods is presented in Part I of this report (Astley et. Al, 2000). Briefly, the birth mothers of children with confirmed prenatal alcohol exposure and a diagnosis of FAS or static encephalopathy were identified retrospectively and prospectively through pediatric diagnostic clinics at the University of Washington and Children's Hospital and Regional Medical Center in Seattle, Washington.

These clinics included the University of Washington FAS Diagnostic Clinic established through this Cooperative Agreement (Clarren and Astley, 1997; Clarren et. al, 2000). The diagnosis of FAS or static encephalopathy/alcohol exposed was made using the clinical gestalt guidelines published by Sokol and Clarren (1989) or the 4-digit Diagnostic Code created by Astley and Clarren (1997, 1999, 2000). Women were eligible to enroll if they gave birth to at least one child with a diagnosis of FAS or static encephalopathy as described above. They could be of any age or race and had to be a resident of Washington State at the time of study enrollment. The women participated in a four-hour structured personal interview developed to generate a lifetime, comprehensive profile of her sociodemographics, reproductive and family planning history, social and health care utilization patterns, adverse social experiences, social support network, alcohol use and treatment history, mental health and intelligence quotient. The interview included 2,044 questions. The questions focused on three time periods in the women's lives: 1) at the birth of the index child with FAS, 2) at the time of the interview and 3) over their lifetime. This study was reviewed and approved by the University of Washington Human Subjects Review Board.

Analysis

t-tests and paired *t*-tests were used to compare outcomes between two independent or paired groups respectively when outcomes were measured on continuous scales. Chi-square tests and Fisher Exact tests were used to compare outcomes between two independent groups when outcomes were measured on nominal scales. Wilcoxon Signed Rank tests and McNemar tests were used to compare proportions between two independent or paired groups respectively, when outcomes were measured on ordinal scales.

RESULTS

Identification and Enrollment of Birth Mothers

A total of 257 women were identified as potentially eligible to enroll in this study. They had given birth to one or more children with confirmed exposure to alcohol and a gestalt diagnosis of FAS (Sokol and Clarren, 1989) or a 4-Digit diagnosis of FAS or static encephalopathy/alcohol exposed (Astley and Clarren, 1997, 1999, 2000). Of the 257 mothers, 92 were confirmed to be eligible to enroll in this study, 58 were confirmed to be ineligible and the eligibility of the remaining 107 remained unknown. Of the 92 mothers confirmed to be eligible, 80 (87%) were enrolled and interviewed. A more detailed summary of identification and enrollment can be found in Part I of this series (Astley *et al*., 2000).

Representativeness of the Maternal and Patient Study Populations

The maternal population that the FAS DPN clinics will target for primary prevention efforts are the birth mothers of children with FAS and static encephalopathy who can be identified and located with reasonable effort and live within Washington State where they are eligible to receive social and health care services. This target population is defined by the eligibility criteria presented above for this study. Eighty of the 92 women (87%) confirmed to be eligible to enroll in this study were enrolled and interviewed. A more detailed summary of the representativeness of this study population is presented in Part I of this series (Astley *et al*., 2000). Based on the percent of women interviewed (87%) and the profiles of the eligible women who did (n = 80) and did not enroll (n = 12), this study population is regarded as being highly representative of the target population.

Profile of the 80 Children whose Mothers were Enrolled.

A profile of the 80 children whose mothers were enrolled in the study is presented in Part I of this series (Astley *et al*., 2000). They were predominantly Caucasian, 7.8 years of age at the time of their diagnosis with over half no longer living with their birth mother at the time of the diagnosis. Eighty-nine percent had a gestalt or 4-Digit diagnosis of FAS or AFAS, the remaining 11% had a 4-Digit diagnosis of static encephalopathy/alcohol exposed without the full FAS facial phenotype. These were the diagnostic outcomes used to determine the birth mothers enrollment eligibility.

Maternal Sociodemographic and Mental Health Profile

A comprehensive, lifetime profile of the 80 birth mothers was generated documenting their sociodemographics, social and health care utilization patterns, adverse social experiences, social support networks and mental health (Tables 1, 2, 3 and 4). Due to the volume of data collected, only selected portions of this profile are presented in this report. Briefly, these women were on average 21 years of age at the birth of their first child, 27 years of age at the birth of the index child, 35 years of age at the diagnosis of the index child and 38 years of age at the time of study enrollment. The study population was predominantly Caucasian, closely resembling the racial distribution of Washington State with a slight over-sampling of Native Americans. Their children were on average 7.8 ± 5.9 (0.1 to 24.2) years of age at the time they were diagnosed. The average maternal I.Q. was 90.0 ± 15.2. Sixty-one percent did not complete high school; 25% had some college education. Fifty-nine percent had a gross annual household income of less than $10,000 at the time of the interview; 78% were in this income bracket at the time of the index child's birth. Ninety-five percent had been physically or sexually abused during their lifetime. Ninety-six percent had one to ten mental health disorders with the most prevalent being post traumatic stress disorder (77 %) and simple phobia (44%).

Maternal Lifetime Reproductive and Family Planning Histories

Their lifetime reproductive and family planning histories are presented in Tables 5 and 6. At the time of the interview, these women had given birth to 272 children. Seventy-three percent of each woman's live births were reportedly unplanned, 76% were reportedly exposed to alcohol. Mean parity and gravity at the time of the interview was 3.4 ± 1.6 and 4.4 ± 2.1 respectively. The mean parity of the index child was 2.6 ± 1.5. Thirty-five of these women went on to have 61 additional children after the birth of their index child. These 35 birth

Table 1. Selected sociodemographic characteristics of the 80 birth mothers

Characteristic	Mean	(S.D.)	Min. - Max.	*n*	Valid (%)
Age (years)					
At time of interview	37.5	(8.1)	23.1 - 55.4	80	
At diagnosis of index child	34.7	(7.3)	20.7 - 52.37	80	
At birth of index child	26.9	(5.6)	17.8 - 40.7	80	
At birth of first child	20.5	(4.1)	11.9 – 32.9	80	
Race/ethnicity					
Caucasian				54	(67.5)
African American				5	(6.3)
Native American/Canadian				20	(24.9)
Hispanic				1	(1.3)
Education: highest level completed (years)					
<9				18	(22.5)
9 - 11				31	(38.8)
12				11	(13.8)
13 +				20	(25.0)
mean	10.8	(2.8)	4 – 17	80	
Estimated IQ from Shipley (1967) Weschler Adult Intelligence Scale - R					
57 - 69				8	(11.1)
70 - 85				20	(27.8)
86 - 100				24	(33.3)
101 - 120				20	(27.8)
Mean	90.9	(15.2)	57 - 120	72	
Reported a religious affiliation				59	(73.7)
Marital status at birth of index child:					
Married / living with partner				50	(62.5)
Separated / divorced				13	(16.3)
Single, never married				17	(21.2)
Stability of housing at birth of index child:					
Permanent, stable				48	(60.0)
Living with friends or relatives				22	(27.4)
Transient, emergency shelters, homeless, jail, drug-free housing				10	(12.6)
Primary source of income at birth of index child:					
Public assistance, unemployment, social security				46	(57.7)
Husband or partner's employment				19	(23.8)
Her own employment				7	(8.7)
Parents, family or other support				8	(9.9)
Gross yearly household income at birth of index child					
Less than $10,000				62	(77.5)
$10,000 to $29,999				14	(17.5)
$30,000 to $69,999				4	(5.0)
Public assistance used at birth of index child (Can select > 1 choice)					
Medicaid/medical assistance				55	(69.6)
WIC				53	(67.1)
Aid for Families with Dependent Child./ welfare				51	(64.6)
Food stamps				50	(63.3)
Social Security Insurance				8	(10.2)

WIC,

Table 2. Maternal report of need for and access to social and health care services around the time of the index child's birth

	Needed Service		Had Sufficient Access To Service	
Characteristic	*n*	Valid (%)	*n*	Valid (%)
Medical care	77	(97.5)	65	(84.4)
Prenatal care	76	(96.2)	61	(80.3)
Medical insurance	75	(94.9)	61	(81.3)
Food donations or assistance	50	(63.3)	41	(82.0)
Childbirth or parenting classes	45	(57.0)	28	(62.2)
Birth control services	43	(54.4)	33	(76.7)
Public health nurse	40	(50.6)	34	(85.0)
Support groups (social, church group, etc.)	37	(46.8)	17	(45.9)
Emergency bill paying services	33	(41.8)	19	(57.6)
Clothing donations	32	(40.5)	26	(81.3)
Mental health services	30	(38.0)	12	(40.0)
Domestic violence services	28	(35.4)	7	(25.0)
Public housing	26	(32.9)	14	(53.8)
Legal assistance	25	(31.6)	10	(40.0)
Vocational classes or job training	19	(24.1)	7	(36.8)
Sexual assault services	8	(10.1)	4	(50.0)

mothers reported that 80% of the 61 children were unplanned and 75% were exposed to alcohol. Although the study did not include gathering include outcome data on these subsequent births, it was known that a least six of these children were diagnosed with FAS. The 80 women on average reported not using any form of birth control during most (81%) of their pregnancies. When asked what form of birth control they would prefer if it were available to them free of charge, the most preferred method was Depo Provera (31.6%) followed by Norplant (16.5%), tubal ligation (13.9%) and the pill (10.1%).

Maternal Lifetime Drug and Tobacco Use

Eighty-six percent of the women reported using illicit drugs at some time in their lives, 40% reported use around the time of the birth of the index child and 9% reported current use (around the time of the interview) (Table 7). The most common drugs used were marijuana, speed/amphetamines and cocaine/crack. Eighty-four percent of the women smoked tobacco around the time of the index child's birth.

Maternal Lifetime Alcohol Use and Treatment Histories

A large volume of data collected on alcohol use and treatment, brief summaries are presented in Tables 8 and 9. Briefly, these women were on average 15 years of age when they first started drinking, between 23 and 28 years of age when they were drinking maximally, 26 years of age when they first attempted to stop drinking and 27 years of age at the birth of the index child. They reported drinking on average nine fluid ounces (or 266 ml) of alcohol per drinking occasion just before the birth of the index child**.** Almost half of the women (47%) reported drinking daily at that time. While 84% reported

Table 3. Home placements and adverse experiences among the 80 birth mothers.

Characteristic	n	(valid %)
Had foster parents	19	(23.8)
Lived in a group home	14	(17.5)
Was ever in a juvenile detention facility	28	(35.0)
Involved in CPS as a child	18	(22.5)
Any of your birth children been in foster care or CPS	64	(80.0)
Sexually abused as a child (<17 yrs)	46	(57.5)
Physically abused as a child (<17 yrs)	37	(46.2)
Emotionally abused as a child (<17 yrs)	79	(98.8)
Sexually abused as an adult (≥17 yrs)	41	(51.3)
Physically abused as an adult (≥17 yrs).	68	(85.0)
Emotionally abused as an adult (≥17 yrs)	69	(86.3)
Sexually and/or physically abused at any time	76	(95.0)

Table 4. Mental health profile of the 80 birth mothers. .

Characteristic	mean	(S.D.)	min. - max.	n	(valid %)
Age (yrs) at onset					
Post-Traumatic Stress	18.9	(9.4)	2 - 41	61	(77.2)
Major Depressive Episode	18.1	(9.6)	3 - 38	47	(59.5)
Phobia – Simple	11.4	(10.5)	2 - 41	35	(44.3)
Phobia - Social	13.9	(7.7)	2 - 38	34	(43.0)
Antisocial Personality	14.2	(5.9)	4 - 30	31	(39.2)
Phobia - Agoraphobia	22.2	(10.3)	2 - 38	29	(36.7)
Generalized Anxiety Disorder	20.7	(10.1)	3 - 37	27	(34.2)
Manic Episode / Bipolar Disorder	18.5	(9.3)	5 - 36	17	(21.5)
Panic Disorder	21.0	(11.4)	4 - 39	16	(20.3)
Bulimia	22.0	(8.3)	7 - 39	10	(12.7)
Schizophrenia / Schizophreniform	20.7	(16.6)	5 - 38	3	(7.0)
Alcohol abuse	19.7	(6.2)	8 - 34	68	(86.1)
Number of women with multiple mental health disorders.					
0 disorders				3	(3.8)
1 disorder				3	(3.8)
2 - 4 disorders				33	(41.3)
5 - 7 disorders				26	(32.5)
8 - 10 disorders				12	(15.0)
Number of mental health disorders per woman		4.7	(2.5)	0 – 10	80
Number of women with mental health disorder(s) at time of interview		39	(48.8)		
Receiving mental health treatment at time of interview				30	(37.5)
Earliest age of onset of mental health disorder(s)					
Childhood (0-8 years old)				33	(44.6)
Adolescent (9-17 years old)				31	(41.9)
Adult (18+ years old)				10	(13.5)
Number of women for which onset of disorder preceded onset of alcohol abuse					
Post-Traumatic Stress				21	(40.4)
Major Depressive Episode				22	(52.4)
Phobia - Simple				23	(76.7)
Phobia - Social				23	(76.7)
Antisocial Personality				21	(70.0)
Phobia - Agoraphobia				7	(29.2)
Generalized Anxiety Disorder				9	(36.0)
Manic Episode / Bipolar Disorder				8	(53.3)
Panic Disorder				7	(43.8)
Bulimia				3	(42.9)
Schizophrenia / Schizophreniform				1	(50.0)

Number of women identified with mental health disorders on the Quick Diagnostic Interview Schedule, age at onset of the disorder and temporal relationship of onset of disorder to onset of alcoholism are given.

they felt they had a problem with alcohol use, 94% reported they did not want to reduce their use because it helped them cope, 72% did not want to reduce because they were in an abusive relationship, and 79% reported they were too depressed to do anything about it. The four most common reasons they did not seek alcohol treatment were they did not want to give up alcohol (87%), they were afraid they would lose their kids (42%), there was no one to take care of the kids (40%) and their partner did not want them to go to treatment (39%).

Of the 80 women interviewed, 41 reported they were abstinent by the time their child was diagnosed with FAS or static encephalopathy. Abstinence was defined as "consumes no alcohol or consumes minimal quantities only on special occasions". This is comparable to the definition of abstinence proposed by Cahalan (*et al*., 1969) "drinks less than once a year or does not drink alcoholic beverages". Fifty of the 80 women reported they were currently abstinent (at the time of the interview). They had made, on average, six concerted attempts to stop drinking. Of the 80 women, 37 (46.2%) were still at risk for producing another child damaged by alcohol exposure at the time of the index child's diagnosis by virtue of still being fertile and actively drinking or at risk for drinking.

Contrasts between Women Who had and had not Achieved Abstinence.

Contrasts between the 50 women who had achieved abstinence by the time of the interview and the 25 women who were not abstinence at this time point are presented in Table 10. The women who had achieved abstinence had, on average, significantly higher I.Q.s, higher household incomes, larger more satisfactory social support networks and were more likely to report a religious affiliation. While they were equally likely to have mental health disorders, those who had achieved abstinence were more likely to have received treatment for their mental health disorder(s). Those who had achieved abstinence reported higher levels of drinking just before the birth of the index child and were more likely to have parents who had problems with alcohol use. They were comparable in race, education, employment, adverse experiences such as physical/sexual/emotional abuse, age at the interview, age at first abstinence attempt, age at first pregnancy, age at birth of index child, and age when first started drinking.

Contrasts between a Woman's Most and Least Successful Abstinence Attempts

Women were asked an identical set of questions about alcohol use and treatment during what they believed was their least successful abstinence attempt, most successful abstinence attempt and the abstinence attempt closest to the birth of the index child. Of the 31 women who were abstinent at the time of the interview and reported a most and least successful abstinence attempt, the following were found to be significantly different between the two attempts. During their most successful attempt, they were on average six years older, more likely to be worried about the impact of their alcohol use on their health, receiving more support from their family, less likely to be employed, more likely to be dependent on public assistance for an income, more likely to be seeking treatment from an agency or person outside their home, more likely to have completed an inpatient program, more likely to have participated in an aftercare program, and more likely to attribute their success in stopping drinking to their desire/readiness to stop and their religious beliefs.

Table 5. Reproductive history of the 80 birth mothers.

Characteristic	Mean	(SD)	Min. - Max.	*n*	Valid (%)
Age (years) at first pregnancy	19.6	(3.8)	12.5 - 30.0	80	
Age (years) at first live birth	20.5	(4.1)	11.9 – 32.9	80	
Age (years) at birth of index child	26.9	(5.6)	17.8 - 40.7	80	
Per woman					
No. of unplanned pregnancies	3.3	(2.0)	0 - 9	80	
No. of unplanned live births	2.5	(1.7)	0 - 8	80	
No. of pregnancies with no birth control	3.5	(2.1)	0 - 9	80	
No. of pregnancies exposed to alcohol	3.0	(1.8)	0 - 8	80	
No. of live births exposed to alcohol	2.4	(1.3)	0 - 6	80	
Proportion of unplanned pregnancies	77.2	(29.2)	0 - 100	80	
Proportion of unplanned live births	73.3	(32.9)	0 - 100	80	
Proportion of pregnancies with no birth control	80.9	(27.6)	0 - 100	80	
Proportion of pregnancies exposed to alcohol	73.2	(30.6)	0 - 100	80	
Proportion of live births exposed to alcohol	75.9	(29.6)	0 - 100	80	
Parity at time of interview (Unit)	3.4	(1.6)	1 - 8	80	
Gravidity at time of interview (Unit)	4.4	(2.1)	1 - 9	80	
Parity of index child (Unit)	2.6	(1.5)	1 - 8	80	
Gravidity of index child (Unit)	3.3	(1.9)	1 - 9	80	
Total no. of children born to the 80 women at the time of the interview				272	
35 women gave birth to 61 children after the birth of the index child. Of these 61 children, the following numbers were:					
Exposed to alcohol.			46	(75)	
Conceived in the absence of birth control			73	(80)	
Diagnosed with FAS (outcomes of other 55 children unknown)			6	(--)	
No. of women who felt there was a time in her life when alcohol use put her at risk for getting pregnant			53	(66.3)	

Table 6. Family planning history of the 80 birth mothers.

			Used Method		Method failed	
Characteristic	Mean	(SD)	*n*	Valid (%)	*n*	Valid (%)
Number of women who had ever used the following types of birth control (Could select > 1 choice*)*						
No method			77	96.3		
Pills			71	88.8	22	31.9
Condoms			57	71.3	13	23.6
Abstinence			42	53.2	0	0.0
Tubal ligation			40	50.0	3	7.5
Withdrawal			25	31.6	8	32.0
Abortion			25	31.3	NA	NA
IUD			20	25.0	4	20.0
Vasectomy			18	22.5	1	5.6
Depo Provera			17	21.3	2	11.8
Diaphragm			14	17.5	3	21.4
Rhythm method			9	11.3	1	11.1
Norplant			7	8.8	0	0.0
Cervical cap			1	1.3	0	0.0
If birth control were available to you free of charge, which method would you prefer to use?						
Depo Provera					25	31.6
Norplant					13	16.5
Tubal ligation					11	13.9
Pills					8	10.1
No method					6	7.6
Condoms					5	6.3
IUD					3	3.8
Foam					3	3.8
Cervical cap					2	2.5
Vasectomy					2	2.5
Rhythm method					1	1.4
Diaphragm, Withdrawal, Abortion					0	0.0
Reasons why you did not use birth control services at some time (may select >1)						
Too involved with alcohol and drugs.					41	51.9
Experienced side-effects from using birth control in the past.					40	50.6
Could not afford it .					34	42.5
Did not have insurance coverage for it .					31	38.8
Partner did not want me to use it.					30	37.5
Had no place to go to get it .					17	21.3
Against my religious beliefs or felt it was wrong.					8	10.1
Age (years) when first started using birth control	18.8	(4.8)			80	

NA, not applicable.

Table 7. Lifetime drug and tobacco use of the 80 birth mothers.

Characteristic	n	(valid %)	n	(valid %)	n	(valid %)
			At time of		Around	
Drug Use		Ever	Interview		FAS Birth	
Alcohol	80	(100.0)	28	(35.0)	77	(96.3)
Marijuana	64	(80.0)	5	(6.3)	17	(21.3)
Speed/amphetamines	51	(63.8)	0	(0.0)	4	(5.0)
Cocaine/crack	50	(62.5)	2	(2.5)	12	(15.0)
Darvon/prescription pain killers	39	(48.8)	1	(1.3)	1	(1.3)
LSD	35	(43.8)	0	(0.0)	0	(0.0)
Valium/tranquilizers	31	(38.8)	0	(0.0)	2	(2.5)
Barbituates/sleeping pills	28	(35.0)	0	(0.0)	2	(2.5)
Inhalants	22	(27.5)	0	(0.0)	1	(1.3)
Heroin/opiates	18	(22.5)	0	(0.0)	6	(7.5)
PCP	16	(20.0)	0	(0.0)	0	(0.0)
Quaaludes	13	(16.3)	0	(0.0)	0	(0.0)
Methadone	9	(11.3)	1	(1.3)	2	(2.5)
Reported no drug use	7	(8.8)	71	(88.8)	47	(58.8)
Tobacco Use						
Ever smoked cigarettes	76	(95.0)	56	(70.0)	67	(84.0)

PCP, LSD?

Table 8. Alcohol use history of the 80 birth mothers

Characteristic	Mean	(SD)	Min. - Max.	*n*	Valid (%)
Mother's age (years)					
When she first started drinking alcohol?	15.1	(4.1)	7 - 30	80	
Range when she was drinking the most:					
Beginning of age range	22.9	(6.7)	10 - 41	78	
End of age range	28.0	(7.9)	14 - 53	75	
When she first tried to stop drinking?	25.8	(7.2)	14.4 - 47.1	74	
At birth of index child	26.9	(5.6)	17.8 - 40.7	80	
At start of most successful abstinence attempt	31.4	(6.8)	19.5 - 52.2	67	
At diagnosis of index child	34.7	(7.3)	20.7 - 52.4	80	
At time of interview	37.5	(8.1)	23.1 - 55.4	80	
Alcohol consumption just before pregnancy with index child					
Usual number of drinks per occasion	18.5	(19.2)	0.0 - 104.0	80	
Type of alcohol consumed most often:					
Wine				8	10.0
Beer				43	53.8
Liquor				21	26.2
Other				8	10.0
Frequency of drinking:					
Daily				35	43.8
Once to several times per week				24	30.0
Once every month or two		2.0		1	26.2
Highest no. of drinks consumed on a single occasion	28.5	(35.9)	3.0 – 26	0.0	73.0
Either birth parent ever had a problem with alcohol				63	78.8
Either grandparent ever had a problem with alcohol				51	63.8
Fertility and abstinence status of each woman at the time of index child's diagnosis					
Not fertile, not currently drinking				24	30.0
Not fertile, but drinking				19	23.8
Fertile, but not currently drinking				17	21.2
Fertile and drinking				20	25.0
Classification of alcohol use at time of interview					
Abstinent				47	62.7
Special occasions only				3	4.0
Social drinking				7	9.3
Problematic drinking				18	24.0
Unknown				5	(--)

[a] 1 drink = 0.5 fluid ounce = 14.8 ml absolute alcohol. Some interpreted 'occasion' to mean a multiple-day binge.

All other factors were comparable between their most and least successful sobriety attempts, including the amount and frequency they were drinking, whether or not they had a partner who was drinking, and the number of children they were caring for at the time.

DISCUSSION

The interviews revealed that this high-risk population of women was diverse in racial, educational and economic background, were often victims of abuse and were challenged by mental health issues. Despite their rather harsh psychosocial profile, many demonstrated the ability to overcome their alcohol dependence over time. Many descriptions of the female alcoholic population have appeared in the literature (Jarvis, 1992). Despite repeated attempts to capture the essence of the "female alcoholic personality syndrome" most have recognized the heterogeneity of the population (Beckman, 1984). In comparing our population to the published profiles of women alcoholics, we find many similarities and some interesting contrasts.

Mental Health

The co-occurrence of alcoholism with other mental health disorders has been widely recognized (Regier *et al.*, 1990; Sheehan, 1993). In 1997, Kessler *et al* (1997) reported on patterns and correlates of psychiatric morbidity and co-morbidity based on data from the National Co-morbidity Survey, a nationally representative household survey of 8,098 men and women between 18 and 54 years of age. Interviews were conducted face-to-face with an 83% response rate. Diagnoses were made according to DSM-III-R using a modified version of the Composite International Diagnostic Interview (WHO, 1990). Lifetime co-occurrence of mental health disorders among the subset of 299 women with diagnoses of alcohol abuse were as follows: post traumatic stress disorder (10.5%), depression (30.1%), simple phobia (28.2%), social phobia (24.1%), antisocial personality (2.1%), agoraphobia (9.3%), generalized anxiety disorder (8.4%), mania (3.8%), and panic disorder (7.3%). The proportion of women with alcohol abuse who had a first onset of a disorder prior to the onset of her alcohol abuse were as follows: post traumatic stress disorder (10.5%), depression (30.1%), simple phobia (28.2%), social phobia (24.1%), antisocial personality (2.1%), agoraphobia (9.3%), generalized anxiety disorder (8.4%), mania (3.8%), and panic disorder (7.3%). Social phobia, simple phobia, depression and drug dependence were

Table 9. Alcohol treatment history of the 80 birth mothers

Characteristic	Mean	(SD)	Min. - Max.	*n*	Valid (%)
Duration of abstinence (years) at time of interview among those who were abstinent	4.6	(5.4)	0.0 - 22.1	50	
Ever felt she had a problem with alcohol				67	83.8
Ever tried to stop or reduce her drinking				75	93.8
Reasons for her not wanting to reduce her alcohol use					
Alcohol helped her cope with life's ups and downs				43	93.5
Too depressed to do anything about it				38	79.2
Was uncomfortable having a problem with alcohol				35	(74.5)
She was in an abusive or violent relationship				33	71.7
Did not think she had a problem				29	60.4
She did not think it would help				20	43.5
Boyfriend/husband/partner did not want her to				17	36.2
Family or friends did not want her to				9	19.6
Reasons that kept her from seeking alcohol treatment					
Did not want to give up alcohol				39	86.7
Was afraid her children would be taken away from her				18	41.9
Boyfriend/husband/partner did not want her to go				17	38.6
There was no one to take care of her kids				17	39.5
Had no money to pay for treatment				15	34.1
Had no insurance or medical care to pay for treatment				12	27.3
She heard bad things about treatment from friends				11	25.0
Was pregnant and afraid the baby would be taken away				11	25.6
Could not get into a program				11	25.0
Too far to travel, she had no transportation				9	20.5
Had a bad experience in past treatment				7	15.9
Was afraid of losing her housing				7	16.3
Family or friends did not want her to go				4	9.1
No. of concerted attempts to stop drinking among women who achieved abstinence at time of interview	6.3	(15.1)	1 - 100	50	
Most successful abstinence attempt (as reported by woman)					
First				13	19.4
Second				17	25.4
Third				17	25.4
Fourth - Tenth				20	25.0
Age (years) at start of most successful attempt	31.4	(6.8)	19.5 - 52.2	67	

highly predictive of subsequent development of alcohol abuse in Kessler's study population. In comparison, the prevalence of mental health disorders in our population of 80 women appeared to be much greater and more likely to precede the onset of their alcohol abuse (Table 4).

Physical/Sexual Abuse

Physical and sexual abuse is prevalent among alcoholic women. Covington (1982) reports that 12% to 53% of alcoholic women report incest or other childhood sexual abuse and up to 74% report some type of childhood or adult sexual abuse. Our study revealed childhood and/or adult sexual abuse occurred in 73% of the 80 women. Almost all (95%) were sexually and/or physically abused during their lifetime. Women who suffer from abuse may become increasingly depressed, anxious, and fearful of violence in their lives (Root, 1989). Root (1989) suggests that many women who relapse following substance abuse treatment are unable to cope with ongoing physical or sexual abuse without using alcohol or other drugs. She contends that substance abuse treatment personnel need to be familiar with the syndrome of domestic violence and abuse, because intervention will be unsuccessful if issues of past and current abuse are not addressed during substance abuse treatment. Beckman (1980) reports that alcoholic women were more likely to report that they felt powerless and inadequate compared to non-alcoholic women. She goes on to state that these findings support the contention that heavy alcohol consumption is a coping mechanism likely to be used by women to relieve feelings of helplessness and powerlessness (Beckman, 1984a). The use of alcohol and other drugs has become a way for women to deal with the emotional pain resulting from earlier abuse by someone close to them, someone they trusted (Covington and Surrey, 1997). Ninety-four percent of the women in our study reported that they did not want to reduce their alcohol use because '*alcohol helped her cope*'. Seventy-two percent reported they did not want to reduce their alcohol use because 'she was in an abusive relationship' or 'she was too depressed to do anything about it' (79%).

Social Support

Social support has often been reported in the literature as an important enabling factor for reduction of alcohol dependence. In a study of 400 Anglo alcoholics in treatment for alcoholism, Beckman, (1984a) reported that females who completed treatment were more likely to have greater social support for treatment entry. The 50 women who achieved abstinence in our study population reported having significantly larger, more satisfactory social support networks than the 25 women who failed to overcome their alcohol dependence.

Table 10. Selected contrasts between the 50 women who had achieved abstinence at the time of the interview and the 25 women who had not achieved abstinence.

	Abstinent at Time of Interview							
	Yes (n = 50)				No (n = 25)			
Characteristic	Mean	(SD)	*n*	Valid (%)	Mean	(SD)	*n*	Valid (%)
Most no. of drinks per occasion								
just before birth of index child**[a]	34.4	(42.4)	48		17.0	(9.6)	22	
Weschler Adult Intelligence Scale-R **	95.9	(13.9)	46		82.0	(12.3)	21	
Marital status at time of interview *								
Married/living with partner			26	52.0			11	44.0
Divorced			6	12.0			9	36.0
Other (widowed, never married)			18	36.0			5	20.0
*Gross yearly household income at interview**								
< US$ 10,000			25	50.0			19	76.0
US$ 10,000 +			25	50.0			6	24.0
Reported a religious affiliation *			36	72.0			11	44.0
Parents had a problem with alcohol use **			44	88.0			16	64.0
Social support network at the time of interview								
No. of support individuals **	17.2	(13.4)	50		11.1	(6.8)	25	
Level of satisfaction with support *[b]	5.4	(1.1)	50		4.7	(1.8)	25	
Mental health disorders								
Generalized Anxiety			16	32.0			11	45.8
Agoraphobia			16	32.0			11	45.8
Social phobia			22	44.0			11	45.8
Simple phobia			21	42.0			12	50.0
Post traumatic stress			38	76.0			19	79.2
Major depression			32	64.0			14	58.3
Mania/Bipolar			12	24.0			5	20.8
Bulimia			7	14.0			2	8.3
Antisocial personality			22	44.0			8	33.3
Number of mental health disorders per woman	5.0	(2.4)	50		4.7	(2.6)	25	
Receiving mental health treatment *			24	52.2			6	26.1

*P< 0.05; ** P< 0.01

[a] 1 drink = 14.8 ml absolute alcohol

[b] Six-point Likert scale (6=most satisfied)

Their social support networks included family, friends and service providers.

Alcohol Treatment

In 1992, a survey was conducted of 79 Seattle and King County non-profit and for-profit alcohol and drug treatment agencies to assess the availability of gender specific treatment for women (Seattle-King County Task Force for Chemically Dependent Women, 1993). The agencies reported 33% of their clientele were women of whom 73% were Caucasian, 14% were African American and 5% were Native American and 73% were between 21 and 40 years of age. Eighty-four percent of the providers did not provide on-site child care, 54% did not offer medical or mental health services at the agency site and 44% did not offer on-site recovery support groups like Alcoholics Anonymous. When the providers were asked what they believed to be the major obstacles for women securing treatment, the top three barriers reported were child-care, money and social stigma. These are certainly troubling statistics in light of the data collected in our study. Ninety-six percent of the 80 women had one or more mental health disorders and the women who received mental health treatment were significantly more likely to achieve abstinence than women with mental health disorders who did not receive treatment. Sixty to 70% of the 80 women reported they were taking care of one or more children during their reported abstinence attempts. Women who achieved abstinence were significantly more likely to participate in an aftercare program like Alcoholics Anonymous. Women who had failed to achieve abstinence had significantly lower incomes.

Beckman and Amano (1984) report that although the relative success of different types of alcoholism treatment has long been debated there is some evidence that treatment programs, regardless of their orientation, produce more positive and lasting outcomes than does doing nothing for the alcohol abuser. It is interesting to note that while 39 of the 50 women who achieved abstinence in our study reported seeking help outside their home during their most successful abstinence attempt, only 31 reported being admitted to an inpatient or/or outpatient program and only 26 reported completing the program(s). Beckman and Amano go on to report that to accept help for an alcohol-related problem, a person generally first must perceive the existence of the problem and be willing to attempt to control the problem. In our study, the women who achieved abstinence were significantly more likely to report concern for their health and a desire to want to stop drinking than the women who did not achieve abstinence.

Beckman and Amaro (1984) report that characteristics related to the individual that affect the person's ability to secure, and inclination to use, services include: 1) individual predisposing factors such as age and ethnicity; 2) attitudes and

beliefs regarding alcohol, treatment and health; 3) personal enabling traits such as personality characteristics and drinking and treatment history; and 4) social enabling characteristics such as child care responsibilities, social support systems and access to financial resources. The predisposing factors of age and ethnicity are immutable. Some mutable predisposing factors such as education and income may be changed through both policy and individual efforts, while other mutable predisposing factors such as religion or marital status, are more often changed through individual decisions (Beckman, 1984). In a study of moderately drinking women entering a program for drinking reduction (Walitzer and Connors, 1997), contrasts between the 120 women who completed the treatment with the 51 women who did not complete the program were comparable to the contrasts observed in our study (Table 10), despite the marked difference in the drinking levels of the two study populations. The moderately drinking women who did not complete treatment were significantly younger, more likely to have a racial background other than Caucasian, more likely to be single or divorced, had fewer years of education and reported more drinking per day at pretreatment relative to the women who did complete the program. Several factors that significantly differentiated the women who did and did not achieve abstinence in our study are potentially mutable (e.g., income, social support network and mental health treatment).

Family Planning

Avoiding alcohol use during pregnancy is just one of two ways to prevent FAS. The other is to prevent pregnancy during alcohol use. While the former reduces health risks to both mother and child, the later is purported by some to be the more simple and immediate means to an end. Both approaches are complex and resistant to change. While society might view the alcohol use and unintended pregnancies of these women as problems in their lives, these women often perceive their alcohol use and pregnancies as partial solutions to their problems. They report that alcohol helps them cope with their often abusive and impoverished lives. Pregnancy and children not only qualify them for social and health care services they might otherwise not receive, it also fulfills an innate desire to bear and raise children. Based on the data collected in this study, it would appear that the women were more successful at avoiding alcohol use than preventing pregnancy. This could be due, in part, to the astonishing lack of access women have to contraceptives. In 1987, 22 years after the U.S. Supreme Court affirmed the legality of contraceptive use in Griswold vs. Connecticut, 57% of pregnancies nationwide were unintended (Forrest, 1994). In 1993-94 new mothers in Washington State had approximately the same frequency of unintended pregnancies resulting in a live birth as the nation as a whole: 40% in Washington compared with 39% nationwide in 1988 (PRAMS, 1996; Brown and Eisenberg, 1995). The women in our study population reported that 78% of their first live born children were the result of unintended pregnancies; 60% of them were exposed to alcohol. There are many reasons why a woman does not practice effective birth control. One reason is access to affordable birth control. In a 1998 survey, conducted by the Office of the Insurance Commissioner, to determine the level of reproductive health benefit coverage in health insurance plans marketed in Washington State, 77% of the insurance plans paid for abortions while only 30% provided coverage for contraceptives. Worse yet, the percentage of individuals actually receiving coverage was lower; four out of five women do not have coverage for contraceptives (Senn, 1998). Lack of access to birth control was not the only reason that women in our study did not use birth control. They were equally likely to report that their alcohol and drug use interfered with their use of birth control and that their partners did not want them to use birth control. Only 10% reported they felt birth control was wrong or against their religious beliefs. In fact, 78 of the 80 women reported using some form of birth control during her life (diaphragm, IUD, cervical cap, pill, Depo Provera, Norplant, condoms, rhythm method or withdrawal) suggesting that few were opposed to birth control.

*Current Status of the Washington State FAS DPN Primary Prevention Prog*ram

The FAS DPN is currently working with the State to facilitate referral of high-risk women identified through the FAS DPN to appropriate primary prevention intervention services. Through this comprehensive approach to FAS diagnosis and prevention, we hope to measurably reduce the incidence of FAS in Washington State.

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MEASURING THE FACIAL PHENOTYPE OF INDIVIDUALS WITH PRENATAL ALCOHOL EXPOSURE: CORRELATIONS WITH BRAIN DYSFUNCTION

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Abstract --- The purpose of this report is to demonstrate how to measure the magnitude of expression of the FAS facial phenotype using the new 4-Digit Diagnostic Code and the previously developed D-Score and to demonstrate how these two measures of the FAS facial phenotype correlate with brain function and structure; correlations that fail to be identified by the older gestalt method of facial measurement. The D-Score and the facial component of the 4-Digit Code quantitatively measure the magnitude of expression of the FAS facial phenotype using three facial features (palpebral fissure length, philtrum smoothness and upper lip thinness). These facial measurement systems were developed by the Washington State FAS Diagnostic and Prevention Network (FASDPN) of clinics and are used to screen and diagnose the facial component of FAS for all patients evaluated in the network of clinics (1,500 to date). The 4-Digit Code is a comprehensive diagnostic system developed by the FAS DPN in 1997 to diagnose the full spectrum of outcomes among patients with prenatal alcohol exposure. The four digits reflect the magnitude of expression of the four key diagnostic features of FAS in the following order: 1) growth deficiency, 2) the FAS facial phenotype, 3) brain dysfunction, and 4) gestational alcohol exposure. The 4-Digit Code was developed to overcome the subjective, highly variable gestalt method of diagnosis that has been used as the standard to date, worldwide. Prior to the development of the 4-Digit Code, the first 445 patients evaluated in the FAS DPN were diagnosed using the gestalt method. For research purposes, their gestalt diagnoses were transformed into 4-Digit Diagnostic Codes, presenting a unique opportunity to directly compare the two diagnostic methods. When the facial phenotype was measured using the 4-Digit Code or D-Score, the magnitude of expression of the FAS facial phenotype was significantly correlated with structural, neurologic and functional measures of brain damage and the phenotype of those receiving a 4-Digit Diagnosis of FAS showed little variability. When the gestalt method of diagnosis was used, the magnitude of expression of the FAS facial phenotype did not correlate with structural, neurologic and functional measures of brain damage and the facial phenotype of those receiving a gestalt diagnosis of FAS was highly variable. The 4-Digit Code and D-Score provide more precise and accurate measures of the FAS facial phenotype and reveal important correlations with brain structure and function, suggesting that intermediate expressions of the FAS facial phenotype may serve as important risk factor for brain damage caused by prenatal alcohol exposure.

INTRODUCTION

Fetal alcohol syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. The syndrome has been broadly characterized by pre- and/or postnatal growth deficiency, a characteristic set of minor facial anomalies, central nervous system (CNS) dysfunction and prenatal alcohol exposure (Jones and Smith, 1973; Clarren and Smith, 1978; Rosett, 1980; Sokol and Clarren, 1989; Stratton *et al*., 1996). In 1997, a new more objective and comprehensive, case-defined method for diagnosing the full spectrum of outcomes in individuals with prenatal alcohol exposure was created called the 4-Digit Diagnostic Code (Astley & Clarren, 1997, 1999, 2000). The four digits of the diagnostic code reflect the magnitude of expression of four key diagnostic features of FAS in the following order: (1) growth deficiency, (2) the FAS facial phenotype, (3) brain damage/dysfunction, and (4) gestational alcohol exposure. Each are ranked independently on a 4-point Likert scale with 4 reflecting severe expression of the feature and 1 reflecting no expression of the feature. The 4-Digit Diagnostic Code is generated by first recording key clinical data on the standardized FAS Diagnostic Evaluation Form and following specific case-definitions to generate each of the four digits (Astley and Clarren, 1999, 2000). The concept of developing a more objective diagnostic system began with the development of a more objective, empirically derived method for measuring and case-defining the FAS facial phenotype (Astley & Clarren, 1996). A discriminant analysis was used to identify the cluster of minor anomalies and their magnitude of expression that best differentiated 42 individuals with FAS from 84 matched controls without FAS. Three features were identified (reduced palpebral fissure/inner canthal distance ratio, smooth philtrum and a thin upper lip). A discriminant equation was generated from the study demonstrating that when the magnitude of expression of these three features results in a discriminant score (D-Score) ≥ 0.80, the facial phenotype was 100% sensitive and specific to FAS. The photographs used to develop this D-Score method of facial analysis were obtained from retrospective sources, thus they did not include internal measures of scale for deriving the true palpebral fissure length (PFL) and innercanthal distance (ICD). The ratio PFL/ICD served as a proxy measure of the true lengths of each feature. Later analyses of direct measures of PFL and inner canthal distance among patients seen in the FAS DPN demonstrated that the key differentiating feature was PFL, not inner canthal distance. Like the D-Score method, the 4-Digit Code uses PFL, philtrum smoothness and upper lip thinness to define the FAS facial phenotype. Unlike the D-Score, a true measure, rather than a proxy measure of PFL, is obtained by either direct measurement or placement of an internal measure of scale in the clinical photograph. The 4-Digit Code method for documenting the magnitude of expression of the FAS facial phenotype serves as both a diagnostic and screening tool.

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The 4-Digit facial rank has and continues to be used to diagnose the facial component of the syndrome in all patients receiving a FAS diagnostic evaluation in the theWashington State FAS Diagnostic and Prevention Network of clinics (n = 1,500 to date). It is also being used to screen all children entering long term foster care in King County WA and all residents in a WA State juvenile rehabilitation facility.

This report illustrates how to measure the magnitude of expression of the FAS facial phenotype using the 4-Digit Code and D-Score and demonstrates how the 4-Digit and D-Score measures of the FAS facial phenotype correlate with brain function and structure; correlations that fail to be identified by the standard gestalt method of diagnosis and facial measurement (Rosett, 1980; Sokol & Clarren, 1989).

SUBJECTS AND METHODS

Study Population

Data for this study came from all patients evaluated in the FAS DPN who met the following inclusion criteria: 1) had a confirmed history of prenatal alcohol exposure (Alcohol 4-Digit Rank = 3 or 4) (Astley & Clarren, 2000) and 2) consented to allow the FAS DPN to use their diagnostic data for research purposes. This study was approved by the University of Washington Human Subjects Division.

FAS Facial Phenotype

Three features (palpebral fissure length, philtrum smoothness and upper lip thinness) are measured to document the magnitude of expression of the FAS facial phenotype (Astley & Clarren, 1996). All other major and minor craniofacial anomalies are measured and recorded for clinical and research purposes but are not used to rank the magnitude of expression of the FAS facial phenotype. Palpebral fissure length is the distance from the endocanthion to the exocanthion (Figure 1). The philtrum furrow is the vertical groove extending from the midline of the upper lip to the nose (Figure 2). The upper lip refers to the area demarcated by the vermilion border (Figure 2). These three features are measured directly by a physician or measured from a digital photograph using image analysis software. Palpebral fissure length is measured in mm and transformed to a standardized z-score using appropriate published normal anthropometric charts (Iosub et al., 1985; Thomas et al, 1987; Hall et al., 1989). The z-score reflects how many standard deviations above or below the population norm the patient's PFL is, based on the patient's age. The z-score is defined as the patient's PFL minus the mean PFL for the normal population divided by the standard deviation of the mean PFL for the normal population. Philtrum smoothness and upper lip thinness are measured on 5-point Likert scales using the pictorial Lip-Philtrum Guide (Figure 3) (Astley & Clarren, 2000). This method for measuring the facial phenotype directly or photographically is demonstrated on a CD-ROM with the aid of animations and video (Astley et al., 1999).

Direct Measurement of Facial Features

Palpebral fissure lengths are measured to the nearest mm with a clear plastic ruler (1 cm by 14 cm in size) held as close as possible to the eye without touching the eye or eye lashes (Figure 1). The FAS DPN chooses not to use calipers because the patients are often too young and active to cooperate safely. The individual is asked to open his/her eyes widely to allow accurate identification of the endocanthion and exocanthion landmarks. The PFL is compared to the normal PFL for age by using a racially appropriate normal chart for PFL to compute the z-score for the right and left PFLs.

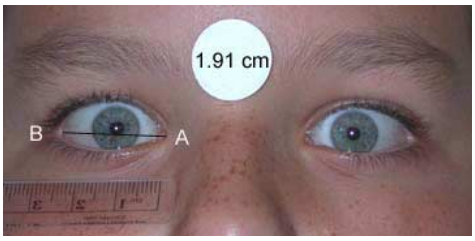

Fig. 1. Palpebral Fissure Length.

Palpebral fissure length (PFL) is measured from the endocanthion (A) to the exocanthion (B). It can be measured directly using a clear plastic cm ruler or it can be measured from a photograph with an internal measure of scale (adhesive paper sticker) placed between the eyebrows or a centimeter ruler placed below the eye.

Fig. 2 . Philtrum and Upper Lip

The philtrum is the vertical groove extending between the nose and the vermilion border of the upper lip. The smoothness of the philtrum and thinness of the upper lip (demarcated by its vermilion border) are measured by selecting the photograph from the Lip-Philtrum Guide (Figure 3) that best matches each feature independently. Upper lip thinness can also be measured from a digital photograph viewed on a computer monitor by tracing the outline of the vermilion border with a mouse and requesting image analysis software like Sigma Scan Pro to compute a measure called circularity (perimeter^2/area) (bottom photo). The thinner the upper lip, the larger the circularity (Figure 3). The circularity scores of the five lips pictured on the Lip-Philtrum Guide assist the physician in selecting the picture that best matches the patient's upper lip thinness. The lip pictured has a circularity of 40.5 and therefore would receive a rank of 1.

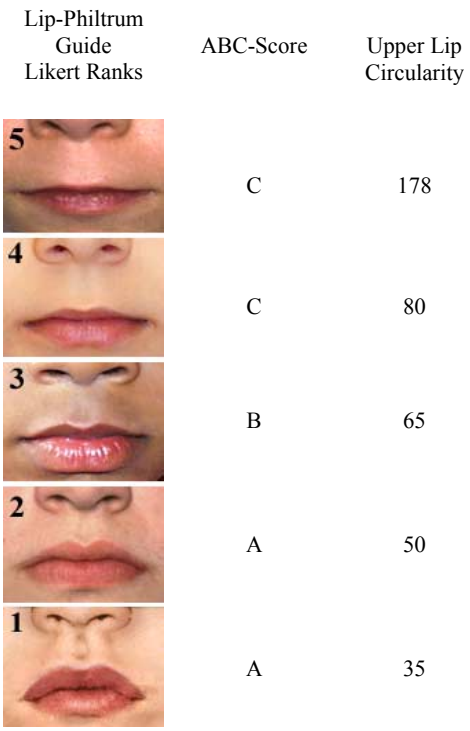

Fig 3. Lip-Philtrum Guide
Pictorial examples of the 5-point Likert scale, upper lip circularity scale and the ABC-scale used to rank upper lip thinness and philtrum smoothness. Circularity (perimeter^2/area) is a continuous measure of upper lip thinness that can be used to facilitate the ranking of upper lip thinness (Figure 2). It is important that the individual's lips are gently closed with no smile (see Figure 5).

Philtrum smoothness and upper lip thinness are measured on 5-point Likert pictorial scales by holding the Lip-Philtrum Guide next to the patient's face and assigning each feature the Likert rank of the photograph that best matches each feature (Figures 3 and 4). Philtrum smoothness and upper lip thinness are ranked independently of one another. For example a child could present with a rank 5 philtrum and rank 1 upper lip. The physician's eyes must be aligned in the patient's Frankfort Horizontal plane (demarcated by a line drawn through the patient's auditory meatus and the lowest border of the bony orbital rim) (Figures 4 and 6). If the physician's eyes are above or below this plane, the upper lip can appear thinner or thicker respectively than it truly is. The patient must have a relaxed facial expression with no smile and lips gently closed. A smile can cause the philtrum and upper lip to appear smoother and thinner than they truly are (Figure 5).

Although the innercanthal distance (R. endocanthion to L. endocanthion) is not used as a diagnostic feature of the FAS facial phenotype, it is still measured to document the presence of hypo- or hypertelorism and it is used as the denominator for the proxy measure

Fig 4. Facial Alignment and Expression

Illustration of a physician aligned in the patient's Frankfort Horizontal plane while using the Lip-Philtrum Guide to rank upper lip thinness and philtrum smoothness. The Frankfort Horizontal plane is defined by a line that passes through the patient's auditory meatus (or the upper edge of the tragus when viewed from the front, Figure 6) and the lowest border of the bony orbital rim (orbitale). The physician's eyes (or camera lens) should be directly in line with the patient's Frankfort Horizontal plane.

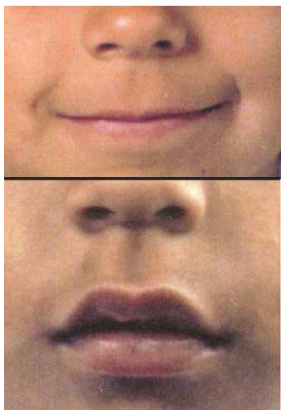

Fig 5. Impact of a Smile on Lip and Philtrum Measures

This is the same individual with (top photo) and without (bottom photo) a smile demonstrating how a smile can erroneously transform a deeply grooved philtrum (Likert rank = 2) and full upper lip (Likert rank = 1, lip circularity = 41) into a smooth philtrum (Likert rank = 4) and thin upper lip (Likert rank 5, lip circularity = 191) (Astley & Clarren, 1996). Circularity (perimeter^2/area) is a continuous measure of upper lip thinness that can be used to facilitate the ranking of upper lip thinness (Figures 2 and 3).

of PFL (namely PFL/ICD) used to compute the facial D-Score when a true measure of PFL is not obtainable. It is measured with a clear plastic ruler and transformed into a z-score using a racially appropriate normal chart for innercanthal distance.

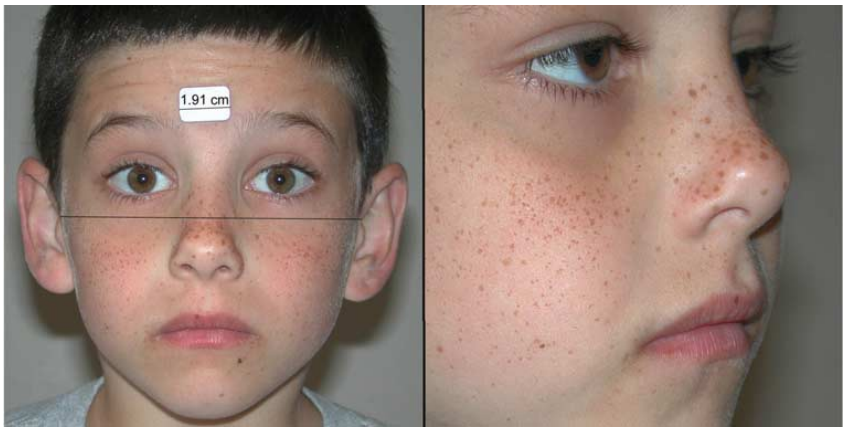

Fig. 6. Standardized Facial Photographs.
Two standardized facial photographs are obtained (frontal, ¾ view) to measure the facial phenotype of FAS. Eyes should be fully open, no eyeglasses, no smile, lips gently closed, and an internal measure of scale placed between the eyebrows. The right and left ears should be equally visible to ensure accurate measurement of the palpebral fissure lengths and innercanthal distance. An imaginary line drawn from the top of the left and right tragus should fall along the patient's lower bony orbital rims confirming the camera is aligned in the patient's Frankfort Horizontal plane (see Figure 4). The ¾ view is obtained to facilitate ranking the philtrum. It is especially important if the camera has a centrally mounted flash that can diminish the appearance of the philtrum depth in a frontal facial photograph.

Photographic Measurement of Facial Features.

An internal measure of scale is placed on the patient's forehead between their eyebrows (Figures 1 and 6). A small, adhesive paper sticker 1/2 inch to 3/4 inch in size serves well and can be purchased from an office supply store. A frontal and ¾ view photograph of the patient's face is obtained using a digital or 35 mm camera. Polaroid cameras do not provide sufficient image resolution. A close-up photo is taken such that the patient's head fills the entire frame (Figure 6). When using a digital camera, a minimum of 3-megapixel resolution is recommended. The lens of the camera is placed in-line with the patient's Frankfort Horizontal plane as described above and illustrated in Figure 4. To judge the Frankfort horizontal plane when viewing the face through the camera, an imaginary line drawn between the upper border of the left and right tragus should fall across the left and right lower bony orbital rim (Figure 6). There should also be no left-to-right rotation of the image; both ears should be equally visible in the frontal photo. The facial expression should be relaxed with no smile, lips gently closed, eyes wide open and no eyeglasses). The ¾ view is taken to facilitate ranking philtrum smoothness by purposely driving a flash of light across the philtrum to see if a shadow is cast. The ¾ view is especially important to obtain if the camera has a centrally mounted flash that can diminish the appearance of a grooved philtrum. Properly aligned facial photographs are obtained in the FAS DPN clinics with a hand-held camera and freestanding patient. Stereotaxic equipment and tripods are not necessary.

The digital image is measured using image analysis software (e.g., Sigma Scan Pro 5, 1999 of FAS DPN software to be distributed in 2001). This software allows one to enlarge the image, enhance the exposure if necessary, makes all the necessary measurements and store the data in an electronic database. If the image is obtained with a 35-mm camera, the slide, print or negative is scanned to generate a digital copy of the image. It is important to note that the resolution (or clarity) of a scanned image as small as a slide or negative may not be sufficiently high. The right and left PFLs are measured by clicking the mouse on the endocanthion and exocanthion landmarks and having Sigma Scan Pro compute the distance between the landmarks in units called pixels (or dots of light on the computer monitor). The length of the internal measure of scale (paper sticker) is also measured in units of pixels. The real size of the PFL in mm is computed from the PFL (in pixels), the length of the paper sticker (in pixels) and the real length of the paper sticker in mm using the following equation:

PFL (mm) = ((length of sticker in mm / length of sticker in pixels) x (PFL in pixels)) x1.07

If the image is rotated right or left, insert the mean PFL in pixels into the equation to compute a mean PFL in mm. The margin of eerror between this mean PFL (mm) and the true mean PFL measureed directly with calipers is less than 1%.

The 1.07 adjustment factor is included in the formula to increase the computed PFL by 7% to adjust for the foreshortening effect of measuring a facial feature that is slightly off the midline of the photograph (Farkas, 1994). This adjustment was confirmed to be accurate by comparing computed PFLs from photographs with measures obtained directly from the subjects with calipers. The computed PFL in mm is transformed into a z-score as described above to standardize it to the population norm. The PFL can also be computed by placing a clear plastic ruler directly under the eye prior to taking the facial photograph (Figure 1). The actual PFL in mm would be computed using the equation above without the adjustment factor.

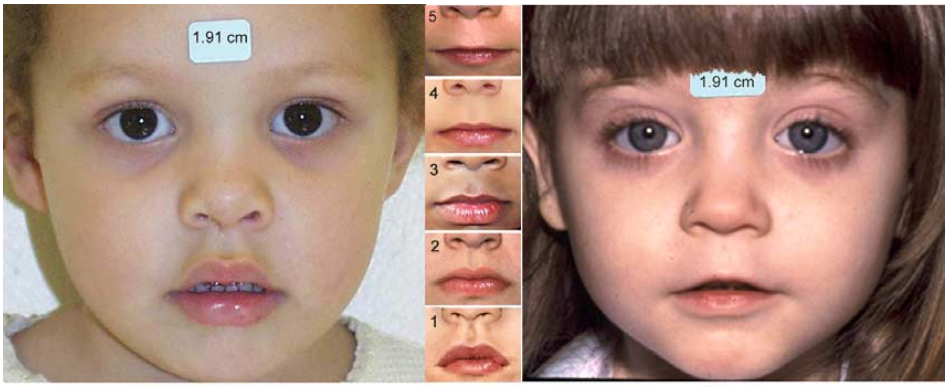

Figure 7. Facial D-Score and 4-Digit Code Rank

Example of the facial D-Scores and 4-Digit Facial Ranks of a control child and a child with the facial phenotype of FAS. The facial D-Score reflects the magnitude of expression of the FAS facial phenotype and is computed when an internal measure of scale is not in the photograph. A D-Score ≥ 0.8 is screen-positive for the face of FAS. The D-Score is computed using the palpebral fissure length/innercanthal distance ratio and the 5-point Likert ranks of philtrum smoothness and upper lip thinness using the Lip-Philtrum Guide pictured in the middle. The 4-Digit Facial rank also reflects the magnitude of expression of the FAS facial phenotype on a 4-point Likert scale. It is computed when the true PFL is available or can be computed. The first step is to generate the ABC-Score reflecting the size of the PFLs, philtrum smoothness and upper lip thinness in that order. Tables 1 and 2 are used to generate the ABC-score and transform it into the 4-Digit Facial Rank. A facial rank of 4 is face of FAS.

The real size of the ICD in mm is computed from the ICD (in pixels), the length of the paper sticker (in pixels) and the real length of the paper sticker in mm using the following equation:

ICD (mm) = (length of sticker in mm / length of sticker in pixels) x (ICD in pixels).

No adjustment factor is added to the equation because the sticker and ICD are on the midline, thus there is no foreshortening error.

Philtrum smoothness and upper lip thinness are measured using the Lip-Philtrum Guide described above. Philtrum smoothness is ranked by holding the Lip-Philtrum Guide next to the image on the computer monitor and selecting the picture that best matches the patient's philtrum. Upper lip thinness is measured by tracing the outline of the vermilion border with the mouse and having Sigma Scan Pro compute a measure called circularity (perimeter^2/area) (Figure 2). Some image analysis software programs call circularity 'compactness'. Circularity ranges from 12.8 for a circle to infinity as the circle is squashed into a line (or becomes thinner). The thinner the upper lip, the larger the circularity (Figure 3). The circularity scores of the five lips pictured on the Lip-Philtrum Guide guide the physician in selecting the picture that best matches the patient's upper lip thinness. The process of taking a facial photograph and measuring the features takes about ten minutes.

Computing the Facial D-Score

The facial D-Score is computed when a true measure of PFL cannot be obtained (e.g., home photos or retrospective photo sets that did not contain an internal measure of scale). The facial D-Score is computed using the equation:

D-score = 0.7408 – (5.7337 x (PFL / ICD)) + (1.1677 x philtrum 5-point Likert rank) + (0.1587 x upper lip 5-point Likert rank).

A facial phenotype with a D-Score ≥ 0.8 is classified as screen-positive for the facial phenotype of FAS (Figure 7). This discriminant function and cutoff value differentiated 42 patients with FAS from 84 controls with 100% sensitivity and specificity in an earlier study (Astley & Clarren, 1996).

Examples of facial D-Scores for a control child and child with the FAS facial phenotype are presented in Figure 7. The D-Score for the 2.8 year-old control child was –2.4 = 0.748 – (5.7337 x (117 pixels / 150 pixels)) + (1.1677 x 1) + (0.1587 x 1). The D-Score for the 2.1 year-old child with the FAS face was +3.2 = 0.748 – (5.7337 x (105 pixels / 143 pixels)) + (1.1677 x 5) + (0.1587 x 5).

Computing the Facial 4-Digit Code Rank

The facial 4-Digit Code rank is the most accurate diagnostic measure of the magnitude of expression of the FAS

Table 1.. 4-Digit Diagnostic Code for Facial Phenotype Rank[a]

A)

Five-Point Likert Scale for Philtrum & Lip	Z-score for mean Palpebral Fissure Length	Palpebral Fissure	Circle the ABC-Scores for: Philtrum	Upper Lip
4 or 5	≤ -2 SD	**C**	C	C
3	>-2 SD and ≤ -1 SD	B	B	**B**
1 or 2	> -1 SD	A	**A**	A

B)

4-Digit Diagnostic Code Rank*	Level of Expression of FAS Facial Phenotype	Palpebral Fissure - Philtrum - Lip ABC-Score Combinations
4	Severe	CCC
3	Moderate	CCB, CBC, BCC
2	**Mild**	CCA, CAC, CBB, CBA, **CAB**, CAA BCB, BCA, BBC, BAC ACC, ACB, ACA, ABC, AAC
1	Absent	BBB, BBA, BAB, BAA ABB, ABA, AAB, AAA

[a]Case definitions used to define the 4-Digit Diagnostic Code ranks for FAS facial phenotype (Astley & Clarren, 2000). A. The first step in deriving the 4-Digit Code rank for the facial phenotype is to derive the facial ABC-Score. For example, if a patient's palpebral fissure lengths were > 2 SD below the norm and their philtrum and upper lip received Likert scores of 2 and 3 respectively (Figure 3), the facial phenotype would receive an ABC-Score of **CAB**. B. The final step is to convert the ABC-Score for Facial Phenotype to a 4-Digit Diagnostic Code Rank. A **CAB** score translates into a 4-Digit Diagnostic Code rank of **2.** This rank would serve as the second digit in the 4-Digit Code.

facial phenotype because it uses the actual PFL rather than the proxy measure (PFL / ICD) used by the D-Score. It can be computed from direct measures or from photographs that contain internal measures of scale. The first step in deriving the facial 4-Digit Code rank is to derive the facial ABC-Score. The magnitude of palpebral fissure length deficiency, philtrum smoothness and upper lip thinness are ranked by circling A, B, or C in each column in the ABC-Score table (Table 1a). The facial ABC-Score is converted to the facial 4-Digit Diagnostic Code Rank using Table 1b.

Examples of facial 4-Digit Code ranks for a control child and child with the FAS facial phenotype are presented in Figure 7. The control child had PFLs equal to 25 mm (z-score = 0), a rank 1 philtrum and rank 1 upper lip. These measures result in an ABC-Score of AAA and a 4-Digit facial rank of 1 (normal). The child with the FAS facial phenotype had PFLs equal to 18 mm (z-score = -4.7), a rank 5 philtrum and rank 5 upper lip. These measures result in an ABC-Score of CCC and a 4-Digit facial rank of 4 (severe). The control child's true PFLs in mm were computed from the photograph with the aid of the internal measure of scale (25 mm = ((19.1 mm / 97 pixels) x (118 pixels)) x 1.07. The PFL z-score = 0 = ((25 mm – 25 mm) / 1.31 mm) (Hall et al., 1989).

The Gestalt FAS Facial Phenotype

Prior to the development of the 4-Digit Code, all patients (n = 462) seen in the FAS DPN were diagnosed using the typical "gestalt" (Sokol & Clarren, 1989) method of diagnosis. The gestalt method uses a less specific qualitative definition for the FAS facial phenotype and records the outcome on a dichotomous scale (present/absent). As reported by Sokol and Clarren (1989) '*A characteristic face is currently qualitatively described as including short palpebral fissures, an elongated midface, a long and flattened philtrum, thin upper lip and flattened maxilla. The specific clinical features will vary with patient age'.* It is rare to find documentation in a patient's medical record or even in the medical literature as to what facial features were present when a diagnosis of FAS was given, thus, if an individual received a gestalt diagnosis of FAS, one can only infer that the FAS facial phenotype described by Sokol and Clarren (1989) was present.

Measures of Brain Function and Structure

Structural (OFC, MRI/CT/PET imaging), neurologic (seizures, cerebral palsy, etc) and functional (standardized psychometric tests of intellect, achievement, adaptation, language, neuropsychological performance, development and behavior) measures of the brain are assessed during the FASDPN diagnostic evaluation. Many of these measures are obtained from the patient's school and medical records; others are collected at the time of the patient's diagnostic evaluation. A few examples of the types of standardized psychometric tests most frequently obtained within each domain include: *Intelligence*: Wechsler Intelligence Scale for Children-3rd Edition (Wechsler, 1996) and Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981), Test of Nonverbal Intelligence (Martin et. al., 1990); *Achievement*: Woodcock-Johnson Psycho-educational Battery (Woodcock & Johnson, 1990), Wide Range Achievement Test (Wilkinson, 1994); *Adaptation*: Vineland Scales of Adaptive Behavior Survey (Sparrow et. al, 1984); *Language*: Test of Word Knowledge (Wiig & Secord, 1992), Test of Auditory Comprehension of Language-Revised (Carrow-Woolfolk, 1985), Peabody Picture Vocabulary Test – Revised (Dunn & Dunn, 1981), Clinical Evaluation ofLanguage Function (Semel et. al., 2000), Test of Language Development-P:3 (Newcomer and Hammill, 2000);

Neuropsychological: Rey Complex Figure Test (Spreen & Strauss, 1998), Tests of Visual-Motor Integration (Beery, 1997), Wide Range Memory and Learning Test (Adams and Sheslow, 2000), California Verbal Learning Test-C (Delis et. al., 1994); *Infant Development*: Bayley Scales of Infant Development (Bayley, 1969), Battelle Developmental Inventory (Newborg et. al., 1984); *Behavior*: Child Behavior Check List (Achenbach, 1991), Conners Parent Rating Scale (Conners, 1985). Due to the age range of the patients and the multiple sources of data, no two patients have an identical, comprehensive set of data. To assess the correlation between the facial phenotype and brain structure and function, three types of brain outcome measures were generated from the FAS DPN clinic database. 1) When a sufficient number of patients had the same standardized assessment performed (e.g., OFC centile, Full Scale Intelligence Quotient, Quick Neurologic Screening Test (a test of soft neurologic signs), Visual Motor Integration) the standardized scores from these assessments served as outcome measures. 2) More typically the clinical data set included a broad array of standardized assessments within and across one or more of the following domains: intelligence, achievement, adaptation, language, sensory processing integration, motor skills, behavioral regulation, memory and infant development. The patient's performance across all tests in each domain was ranked on a 4-point Likert scale. The ranks were defined as follows: 0 (no tests conducted*, most likely because child was too young*) 1 (all test outcomes were in the normal range; no test score was lower than 0.9 S.D.s below the norm), 2 (one or more test outcomes were in the borderline range, between 1.0 S.D. and 1.9 S.D. below the norm, but no test was two or more S.D.s below the norm) and 3 (one or more tests were below normal, defined as two or more S.D.s below the norm). 3) Finally, the 4-point Likert Scale used by the 4-Digit Code to rank evidence of organic brain damage was used as a global composite measure of brain structure and dysfunction. The case-definitions and clinical names applied to each rank are: Rank 4 (microcephaly or abnormalities on brain images or evidence of persistent neurologic findings or an IQ <= 60); Rank 3 (performance on standardized psychometric tests > 2 SD below the norm across three or more of the following areas: sensory processing/integration, motor skills, behavioral regulation, adaptive behavior, memory, language, achievement, intelligence); Rank 2 (observational data strongly suggests the possibility of brain damage, but data does not permit a Rank 3 or 4 classification); Rank 1 (no evidence of problems likely to reflect brain damage). The FAS DPN assigns the clinical term static encephalopathy to Brain Ranks 3 and 4 and neurobehavioral disorder to Brain Rank 2. More detailed definitions of these terms are presented in Astley and Clarren (1999, 2000).

Prenatal Alcohol Exposure

All patients in this study had a confirmed history of prenatal alcohol exposure (4-Digit Alcohol Rank = 3 or 4) (Astley and Clarren, 1999, 2000). A history was considered confirmed if the birth mother reported consumption of alcohol during pregnancy, another individual directly observed the birth mother drinking during pregnancy and/or there was information available in the medical records that confirmed the birth mother had been drinking during pregnancy (e.g., blood alcohol concentrations, reported intoxicated at the time of delivery, etc). During the diagnostic evaluation, the following maternal alcohol use information is recorded on a standardized Diagnostic Evaluation Form: average and maximum number of drinks per drinking occasion just before and during pregnancy, average number of days she drank per week just before and during pregnancy, type of alcohol consumed, trimester(s) in which alcohol was consumed, was she ever diagnosed with alcoholism, did she ever receive treatment for alcoholism and finally, what was the source and reliability of the above reported information.

Statistical Analyses

Descriptive statistics were used to summarize the profile of the study population. Pearson correlation coefficients were computed to assess correlations between outcomes recorded on continuous scales. Regression analysis was used to determine if significant Pearson correlations were influenced by covariates such as age and gender. Chi-square tests were used to assess trends between outcomes recorded on nominal and ordinal scales. Oneway ANOVA with post hoc tests for linear trends was used to compare mean outcomes across three or more groups. Stepwise discriminant analysis (maximizing Wilk's lambda) was used to identify the facial feature(s) that best differentiated patients with and without FAS diagnosed using the gestalt and 4-Digit Code methods. Prior probability of FAS was set equal to the prevalence in the study samples. The probability of F to enter was 0.05, and F to remove was 0.10. The unstandardized canonical discriminant function coefficients were computed to derive the discriminant equation for calculation of each subject's discriminant score. The discriminant score was used to predict each subject's diagnostic classification (FAS, not FAS). The predicted diagnosis was compared to their actual diagnosis to compute sensitivity and specificity.

RESULTS

Sociodemographic Profile of Study Population

Of the 1,130 patients evaluated in the FAS DPN clinics through 1999, 952 (84%) had a confirmed history of prenatal alcohol exposure (4-Digit alcohol rank = 3 or 4). All had given consent to use their data for research. A brief sociodemographic profile of this study population is presented in Table 2. The population was 49% Caucasian, 44% female with an average age of 9.2 ± 6.7 S.D. years. Using the 4-Digit Diagnostic Code, 76 (8%) had a 4-Digit diagnosis of FAS or Atypical FAS (FAS without growth deficiency) and 767 (81%) had a 4-Digit diagnosis of static encephalopathy or neurobehavioral disorder without the full physical features (growth deficiency and/or facial phenotype) of FAS. A subset of 462 patients received a FAS diagnostic evaluation using the gestalt method prior to the development of the 4-Digit Code. The sociodemographic profile of this subgroup of 462 is comparable to the entire study population of 952 patients. The gestalt method of diagnosis had been carried out by one of three dysmorphologically-trained pediatricians (a dysmorphologist (SKC), a geneticist and a developmental pediatrician).

Table 2. Sociodemographic profile of patient population with confirmed prenatal alcohol exposure.

Characteristics		Entire Study Sample	Gestalt Subset
		(n = 952)	(n = 462)
Age (yrs.), mean (SD), range		9.2 (6.7) 0.2 to 50.8	9.4 (6.6) 0.2 to 50.8
Race, n (%)			
Caucasian		463 (48.5)	231 (50.0)
African American		120 (12.6)	44 (9.5)
Native American/Alaskan/Canadian		229 (24.1)	113 (24.5)
Other		141 (14.8)	74 (16.0)
Gender, n (%)			
female		418 (43.9)	194 (42.0)
4-Digit Diagnostic Code diagnostic category[a], n (%)			
FAS[1] 28 (2.9)		10 (2.2)	
Atypical FAS[2]		48 (5.0)	17 (3.7)
Static encephalopathy, not FAS[3]		295 (31.0)	139 (28.1)
Neurobehavioral disorder, not FAS[4]		482 (50.7)	256 (55.5)
Other[5]		99 (10.4)	49 (10.6)
Facial Phenotype			
D-Score, mean (SD)		-0.9 (1.7)	-1.2 (1.8)
4-Digit Code, n (%)			
Absent (1)		215 (22.6)	93 (20.1)
Mild (2)		544 (57.1)	285 (61.7)
Moderate (3)		100 (10.5)	45 (9.7)
Severe (4)		93 (9.8)	39 (8.4)
Reported Prenatal Alcohol Exposure			
Just Prior to Pregnancy			
Ave. number of drinks[b] per occasion, mean (SD)	9.9 (10.9)	9.5 (6.8)	
Number of drinking days per week, mean (SD)		4.6 (2.2)	4.5 (2.3)
During Pregnancy			
Ave. number of drinks[b] per occasion, mean (SD)	8.5 (10.2)	8.0 (6.8)	
Number of drinking days per week, mean (SD)		4.5 (2.4)	4.4 (2.4)

a. Astley & Clarren, 2000: 1) 4-Digit Diagnostic Category A; 2) 4-Digit Diagnostic Category C; 3) 4-Digit Diagnostic Categories E and F; 4) 4-Digit Diagnostic Categories G and H; 5) 4-Digit Diagnostic Categories I and J; b. A drink equals 0.5 fluid ounces. Absolute alcohol.

Correlations between FAS facial phenotype and brain structure/function

The magnitude of expression of the FAS facial phenotype, when measured using the D-Score and the 4-Digit Code, correlated significantly with structural, neurologic and functional measures of brain damage (Tables 3 and 4). When the magnitude of expression of the FAS facial phenotype increased, OFC percentile decreased, the Quick Neurological Screening Test standard score increased (a high score reflects neurologic dysfunction), the FSIQ decreased, and composite measures of language and early childhood development were more dysfunctional or delayed. The 4-Digit Diagnostic ranks for the magnitude of expression of the facial phenotype and evidence of brain damage (measured independently during the diagnostic evaluation) were also correlated. As the magnitude of expression of the FAS facial phenotype increased from 1 (normal) to 4 (severe FAS), the proportion of patients with evidence of organic brain damage (structural, neurological and/or functional) increased significantly. When the 4-point Likert scale for brain is collapsed into the three clinical categories (Rank 1, no evidence of brain damage; Rank 2, neurobehavioral disorder and Ranks 3 and 4, static encephalopathy) the correlation between the magnitude of expression of the facial phenotype and brain dysfunction increased. The 4-Digit and D-Score measures of the magnitude of expression of the FAS facial phenotype were not influenced by age, race or gender. In contrast to the 4-Digit and D-Score measures of the FAS facial phenotype, the gestalt measure of the FAS facial phenotype did not correlate with any measures of brain structure or function in this study population.

Correlations between FAS facial phenotype and alcohol exposure

The magnitude of expression of the FAS facial phenotype measured by the D-score and 4-Digit facial rank increased significantly with increasing number of days of maternal drinking per week both before and during pregnancy. For example, as the 4-Digit facial rank increased from 1 (normal) to 4 (severe FAS), the mean number of days per week the birth mother drank during pregnancy increased from 4.0 to 4.4 to 4.9 to 4.8 respectively ($F = 7.6$ weighted linear term, $p = 0.006$). The Pearson Correlation Coefficient between the facial D-Score and the number of days per week the birth mother drank during pregnancy was +0.11, $p = 0.009$.

Variability of the FAS facial phenotype

When patients were diagnosed using the gestalt method, the facial phenotype of those receiving a gestalt diagnosis of FAS was highly variable (Table 5). In contrast, when the same patients were diagnosed using the 4-Digit Code, the facial phenotype among those receiving a 4-Digit diagnosis of FAS showed little variability. Of the 462 patients who received diagnostic evaluations using both the gestalt and 4-Digit Code methods, 445 had sufficiently complete data sets for inclusion in the following descriptive comparison of the gestalt and 4-Digit code methods of diagnosis.When the gestalt method was used, 52 of the 445 patients (11.7%) received a diagnosis of FAS. When the 4-Digit Code method was used, 10 of the 445 patients (2.2%) received a diagnosis of FAS.

Table 3. Correlations between 4-Digit Rank of FAS facial phenotype and brain structure/function.

	4-Digit Rank of FAS Facial Phenotype								p
Brain Structure and Function	1:Normal		2:Mild		3:Moderate		4:Severe		value
OFC centile: mean (SD)	51.2	(4.4)	51.9	(4.0)	50.5	(3.0)	50.3	(4.4)	**
Full Scale IQ: mean (SD)	89.9	(15.7)	85.4	(15.6)	84.0	(17.8)	79.5	(14.9)	**
QNST standard score: mean (SD)	26.9	(17.9)	33.0	(15.3)	42.2	(14.0)	39.0	(19.7)	*
CBCL external T: mean (SD	72.2	(10.1)	70.4	(10.7)	70.4	(8.1)	65.3	(11.8)	*
Language: n (%)									
Normal (above -1 SD)	75	(49.7)	147	(34.9)	28	(35.0)	15	(23.4)	***
Borderline (-1.0 SD to –1.9 SD)	38	(25.2)	120	(28.5)	28	(35.0)	22	(34.4)	
Clinical (≥ 2 SD below norm)	38	(25.2)	154	(36.6)	24	(30.0)	27	(42.2)	
Infant Development: n (%)									
Normal (above -1 SD)	25	(47.2)	43	(26.9)	7	(19.4)	8	(22.2)	**
Borderline (-1.0 SD to –1.9 SD)	10	(18.9)	55	(34.4)	12	(33.3)	11	(30.6)	
Clinical (≥ 2 SD below norm)	18	(34.0)	62	(38.8)	17	(47.2)	17	(47.2)	
Brain damage: n (%)									
4-Digit Rank: Likelihood (evidence)									
1: Unlikely	45	(20.9)	42	(7.7)	6	(6.0)	4	(4.3)	***
2: Possible (caregiver report)	116	(54.0)	291	(53.7)	51	(51.0)	24	(25.8)	
3: Probable (psychometric)	31	(14.4)	110	(20.3)	15	(15.0)	29	(31.2)	
4: Definite (struct./neurologic)	23	(10.7)	99	(18.3)	28	(28.0)	36	(38.7)	
Brain damage: n (%)									
4-Digit Rank: Diagnostic Name.									
1: Normal	45	(20.9)	42	(7.7)	6	(6.0)	4	(4.3)	***
2: Neurobehavioral disorder	116	(54.0)	291	(53.7)	51	(51.0)	24	(25.8)	
3&4: Static encephalopathy	54	(25.1)	209	(38.6)	43	(43.0)	65	(69.9)	
Age (yr.) at diagnosis: mean (SD)	8.3	(6.7)	10.1	(6.4)	8.6	(7.9)	7.6	(5.5)	

OFC: occipital frontal circumference; QNST: Quick Neurologic Screen Test; CBCL: Child Behavior Check List
* (p-value < .05) ** (p-value < .01) *** (p-value < .001)

Table 4. Correlations between FAS Facial D-Score and brain structure/function.

Brain Structure/Function				
	Pearson Correlation Coefficient		n	p-value
OFC centile:	-0.19		901	***
Full Scale I.Q.	-0.18		405	***
Verbal I.Q.	-0.13		296	*
Performance I.Q.	-0.23		300	***
Quick Neurologic Screen Test:	+0.42		64	***
	Mean D-Score[a]	(SD) D-Score	n	p-value
Language				
Normal (>-1 SD)	-1.1	(1.6)	260	*
Borderline (-1.0 SD to –1.9 SD)	-0.7	(1.7)	199	
Clinical (≥ 2 SD below norm)	-0.7	(1.8)	235	
Early Infant Development				
Normal (>-1 SD)	-0.8	(1.6)	78	*
Borderline (-1.0 SD to –1.9 SD)	-0.5	(1.8)	86	
Clinical (≥ 2 SD below norm)	-0.3	(1.8)	109	
Brain damage/dysfunction				
4-Digit Rank: Likelihood (source of evidence)				
1: Unlikely	-1.5	(1.6)	88	***
2: Possible (caregiver report)	-1.1	(1.6)	466	
3: Probable (psychometric)	-0.7	(1.7)	181	
4: Definite (structural/neurologic)	-0.1	(1.9)	174	
Brain damage/dysfunction				
4-Digit Rank: Diagnostic Name				
1: Normal	-1.5	(1.6)	88	***
2: Neurobehavioral disorder	-1.1	(1.6)	466	
3 and 4: Static encephalopathy	-0.4	(1.9)	355	

OFC: occipital frontal circumference; * (p-value < .05) ** (p-value < .01) *** (p-value < .001)
a. The higher the D-score, the more FAS-like the facial phenotype.

Table 5. Comparison of gestalt and 4-Digit FAS facial phenotype classifications among the 445 patients who received both a gestalt and a 4-Digit Diagnosis.

Feature	Gestalt Diagnosis				4-Digit Code Diagnosis			
	FAS		Not FAS		FAS[1]		Not FAS[2]	
	52		393		10		435	
Palpebral fissure length z-score:n (%)								
Normal (> -2 S.D.)	5	(9.6)	143	(36.4)	0	(0.0)	148	(34.0)
Small (-2 S.D. to –2.99 S.D.)	8	(15.4)	98	(24.9)	0	(0.0)	106	(24.4)
Very small (≤ -3 SD)	39	(75.0)	152	(38.7)	10	(100.0)	181	(41.6)
Upper lip thinness 4-Digit Rank[3]: n (%)								
1. Very thick	5	(9.8)	137	(35.5)	0	(0.0)	142	(33.2)
2. Moderately thick	9	(17.6)	47	(12.2)	0	(0.0)	56	(13.1)
3. Average	14	(27.5)	76	(19.7)	0	(0.0)	90	(21.0)
4. Moderately thin	9	(17.6)	83	(21.5)	2	(20.0)	90	(21.0)
5. Very thin	14	(27.5)	43	(11.1)	8	(80.0)	50	(11.7)
Philtrum smoothness 4-Digit rank[3]: n (%)								
1. Deeply grooved	8	(15.7)	197	(51.0)	0	(0.0)	205	(47.9)
2. Moderately grooved	7	(13.7)	82	(21.2)	0	(0.0)	89	(20.8)
3. Average	14	(27.5)	67	(17.4)	0	(0.0)	81	(18.9)
4. Moderately smooth	8	(15.7)	31	(8.0)	1	(10.0)	38	(8.9)
5.Very smooth	14	(27.5)	9	(2.3)	9	(90.0)	15	(3.5)
FAS facial 4-Digit Rank: n (%)								
1. No FAS features	1	(1.9)	92	(23.4)	0	(0.0)	93	(21.4)
2 Mild FAS features	27	(51.9)	258	(65.6)	0	(0.0)	285	(65.5)
3. Moderate FAS features	10	(19.2)	29	(7.4)	0	(0.0)	39	(9.0)
4. Severe FAS features	14	(26.9)	14	(3.6)[4]	10	(100.0)	18	(4.1)[5]
FAS Facial D-Score[6]: mean (SD)	0.6	(1.8)	-1.5	(1.5)	2.9	(0.7)	-1.4	(1.6)
Epicanthal folds[7]: n (%)	11	(26.2)	75	(28.5)	2	(28.6)	84	(28.9)
Hypertelorism: n (%)	0	(0.0)	13	(3.4)	0	(0.0)	14	(3.3)
Hypotelorism: n (%)	1	(2.0)	28	(7.3)	0	(0.0)	29	(6.8)
Clown eyebrows: n (%)	6	(15.0)	20	(8.2)	2	(20.0)	7	(2.5)
Flat nasal bridge: n (%)	3	(7.1)	12	(4.7)	2	(20.0)	13	(4.5)
Ptosis: n (%)	9	(22.0)	30	(12.0)	2	(20.0)	6	(1.1)
Flat hypoplastic midface: n (%)	8	(19.0)	17	(7.6)	0	(0.0)	25	(9.7)
Age (yr) at diagnosis: mean (SD)	9.7	(6.2)	9.4	(6.6)	7.4	(5.6)	9.5	(6.6)

(1) 4-Digit diagnostic categories A and B (Astley & Clarren, 2000); (2) 4-Digit Diagnostic categories E-V (Astley & Clarren, 2000); (3) See Figure 3; (4) 9/14 patients ≤ 5 yrs. old; (5) all patients ≤ 5yrs. old, thus too young to confirm brain dysfunction and diagnose as FAS yet; (6) D-Score ≥ 0.8 = FAS facial phenotype; (7) increasing severity of epicanthal folds are significantly associated with decreasing age F = 8.2, p = 0.004.

Of the 52 patients who received a gestalt diagnosis of FAS, only 34% had growth deficiency (height and weight below the 10th percentile), only 27% had the full FAS facial phenotype (as defined by Rank 4 in the 4-Digit Code) and only 52% had psychometric, structural and/or neurological evidence of brain damage. In contrast 100% of the 10 patients with a 4-Digit Code of FAS had growth deficiency, the full FAS facial phenotype and evidence of brain damage as defined in the sentence above. The magnitude and frequency of expression of nine minor facial anomalies frequently reported to be associated with the gestalt FAS facial phenotype were compared between the patients who did and did not receive a diagnosis of FAS using the two diagnostic methods (Table 5). The prevalence of all other minor anomalies was relatively low. Hypertelorism (an innercanthal distance greater than 2 S.D.s above the norm), often referred to in the literature as a diagnostic feature of FAS, was not observed in any of the 52 patients with either a gestalt or 4-Digit diagnosis of FAS. The most prevalent minor anomaly in the gestalt group was small palpebral fissure lengths. When the same patients were diagnosed using the 4-Digit Code, the facial phenotype of the patients who received a diagnosis of FAS did not vary from patient to patient. All patients diagnosed with FAS had small palpebral fissures, a smooth philtrum (Rank 4 or 5) and a thin upper lip (Rank 4 or 5).

Stepwise discriminant analyses performed on the subset of patients who received both gestalt and 4-Digit diagnostic evaluations further confirmed that the FAS facial phenotype was highly variable when the gestalt method was used and showed little variability when the 4-Digit Diagnostic Code method was used. The following facial features were made available to the stepwise discriminant analyses: mean PFL z-score, innercanthal distance z-score, mean PFL/innercanthal distance ratio, lip thinness measured on 5-point Likert scale, philtrum smoothness measured on 5-point Likert rank, epicanthal folds, flat nasal bridge, hypoplastic midface, ptosis, clown eyebrows, and nose length to midface height ratio. Only patients who had all of these facial descriptors measured in their data sets were included in the analyses. Among the 431 patients who received a gestalt diagnostic evaluation, the stepwise discriminant analysis was unable to identify a pattern of facial anomalies that accurately differentiated the 52 patients who received a gestalt diagnosis of FAS from the 379 who did not receive a gestalt diagnosis of FAS. Two features did meet the stepwise entry criteria for inclusion into the discriminant equation: the PFL/innercanthal distance ratio and philtrum smoothness. These two features, however, were only able to differentiate the 52 with FAS from the 379 patients without FAS with 97.6% specificity (364 of 379 without FAS were correctly classified as not having FAS) and 37.3%

sensitivity (only 19 of the 52 with FAS were correctly classified as having FAS). In contrast, when the same patients were diagnosed using the 4-Digit Code, the discriminant analysis identified three facial features (PFL z-score, philtrum smoothness and upper lip thinness (both measured on the 5-point Likert scale from the Lip-Philtrum Guide)) as the features that differentiated the 10 patients with a 4-Digit diagnosis of FAS from the 411 patients that did not receive a 4-Digit diagnosis of FAS with 100% sensitivity and specificity.

DISCUSSION

The 4-Digit Code and D-Score methods for measuring and reporting the magnitude of expression of the FAS facial phenotype offer many advantages over the gestalt method. The use of a specifically case-defined diagnostic method that relies on objective, quantitative, higher-level measurement scales: 1) facilitates the collection of more accurate and precise outcome measures by a broader array of medical professionals, 2) establishes a common descriptive language for more clearly communicating outcomes in medical records and in the medical literature and 3) provides more power to detect clinically important associations-associations that are at risk of being missed when more subjective, qualitative, nominal measurement scales are used. Noted experts in dysmorphology and anthropometry have long stressed the importance of collecting more accurate, objective measures of facial anomalies in syndrome identification (Feingold, 1975; Farkas, 1994).

The facial anomalies used to generate the 4-Digit and D-Score measures of the FAS facial phenotype were identified by multivariate discriminant analyses and found to be highly sensitive and specific to FAS and prenatal alcohol exposure (Astley and Clarren, 1996). In contrast, the gestalt approach relies on anomaly checklists that purportedly characterize the FAS facial phenotype, leaving it up to the physician or researcher to arbitrarily select which anomalies define the phenotype, how many must be present and how severe they must be expressed (Rosett, 1980; Sokol and Clarren, 1989; Wiedemann et. al., 1989; Gorlin, 1990; Jones, 1997). This approach has lead to highly variable outcomes with no documented sensitivity or specificity to prenatal alcohol exposure (CDC, 1993; Floyd et. al., 1994). Consider the following series of studies that utilized anomaly checklists to address an important diagnostic question "Does the FAS facial phenotype diminish with age?" In a follow-up study of 54 patients Spohr and Steinhausen (1987) reported a statistically significant reduction in facial features defined as "characterizing the craniofacial dysmorphology" of FAS (epicanthal folds, blepharophimosis, ptosis, short upturned nose, high arched palate/cleft palate and retrognathia). The one feature that did not change with age was a thin upper vermilion. PFL and philtrum smoothness were not measured. In a retrospective study of 200 alcohol-exposed children Majewski (1993) reported that in elder cases the nose was no longer short and upturned, the lips were no longer thin and the chin often became rather prominent. The one feature that did not change with age was short palpebral fissure lengths. Finally, in a 10-year follow-up study of eight of the first eleven children to be diagnosed with FAS, Streissguth (et al., 1985) reported that while some craniofacial features changed with age (nasal bridges became more prominent and mandibles became relatively prognathic), other did not change with age (palpebral fissures remained short, philtrums remained hypoplastic, the vermilion border of the upper lip remained thin and the midface remained flat). From these and similar studies, the 1996 report by the Institute of Medicine concludes "*that some FAS craniofacial anomalies may be less evident at birth, become more conspicuous during early infancy and childhood, and often diminish or even disappear during adolescence and adulthood*" (Stratton et al., 1996). But most of the features that were reported to diminish with age 1) have never been confirmed to be sensitive or specific to prenatal alcohol exposure and 2) are remarkably consistent with descriptions of normal facial growth. Enlow and Hans (1996) report that when one compares the face of a normal child to that of a normal adult, the child's nose is short and upturned, the nasal bridge is low and the mandible is small and retrusively placed. Interestingly, the features that were least likely to change with age (short PFL, smooth philtrum and a thin upper lip) are the only features confirmed to be sensitive and specific to prenatal alcohol exposure in our previous (Astley and Clarren, 1996) and current studies and match the features originally identified as defining the face of FAS by David Smith back in 1979. As stated by Smith (1979) "*As far as the diagnosis is concerned, perhaps the most important point to emerge in the last few years is that the facial abnormalities seen in affected infants are the key cluster of features that tend to make FAS a clinically discernible entity. Many disorders result in mental and growth deficiency, but in FAS the deficiencies are typically present in a patient whose face has short palpebral fissures, a hypoplastic upper lip with a thinned vermilion border and a smoothed or absent philtrum. Up to now, the descriptions of the facial features of FAS that have appeared in the literature have not always emphasized the same abnormalities. This has led to some confusion, but inspection of the photographs accompanying these reports leaves no doubt about the facial similarities of FAS patients*.". While clinical judgement plays an important role in the initial identification and definition of a new syndrome, more analytic approaches to pattern recognition such as discriminant analysis, supported by objective, quantitative measures of outcome, can and should be used to hone the definition. The match between the facial features identified by our descriminant analyses and reported by Smith back in 1979 further demonstrates that the analytical approach used by the FAS DPN has succeeded in objectively case-defining not redefining the original FAS facial phenotype.

Correlations between face and brain

The correlations observed between the magnitude of expression of the FAS facial phenotype and brain structure and function: 1) further validate that short PFLs, a smooth philtrum and a thin upper lip are key diagnostic facial features, 2) are consistent with the clinical literature that midline defects can *predict* underlying brain dysfunction (DeMeyer, 1975; Astley et al., 1999) and 3) provide evidence that an intermediate expression of the FAS facial phenotype may serve as an important clinical risk factor for brain damage caused by prenatal alcohol exposure. The FAS facial features (short palpebral fissure lengths, a smooth philtrum and a thin upper lip) selected by the discriminant analyses in this study and the previous study (Astley & Clarren, 1996) are midline anomalies

derived from the anterior frontal neural crest primordia of the early forebrain (Johnston, 1975). Deficiencies in the numbers of crest cells most frequently affect development of the frontonasal derivatives and are usually associated with defective forebrain and eye development (Johnston, 1975). It has long been speculated that some extreme forms of midline facial anomalies (i.e., cyclopia, holoprosencephaly, arhinencephaly) are pathognomonic of brain malformation (DeMeyer, 1975). This speculation was further supported by the presence of a proportional increase in midventral forebrain deficiencies and the severity of facial dysmorphia in mice and a nonhuman primate with holoposencephaly, all of which were exposed to ethanol early in gestation (Sulik & Johnston, 1982, 1983; Sulik, 1984; Siebert et al., 1991). Now, two additional studies have demonstrated that much more subtle midline facial anomalies (craniofacial bony alterations in nonhuman primates and soft-tissue facial anomalies in this current human clinical population) appear to be pathognomonic of brain malformation/dysfunction (Astley & Clarren, 1999). David Smith (1979) reported similar findings "*the severity of dysmorphic features appears to be related to the degree of mental deficiency*". The dysmorphic features he was referring to were small palpebral fissures, a smooth philtrum and a thin upper lip. No other studies, to our knowledge, have reported significant linear correlations between the magnitude of expression of the FAS facial phenotype and cognitive impairment among individuals with prenatal alcohol exposure. Other clinical research teams have reported correlations between the number of physical anomalies observed over the entire body and brain dysfunction in individuals with prenatal alcohol exposure, although not all were reported to be statistically significant (Majewski, 1993; Spohr et al., 1993). No correlations were observed between the gestalt FAS facial phenotype and brain dysfunction in this study. Failure to detect statistically significant correlations between face and brain, when a gestalt approach to diagnosis was used, has also been reported by others (Graham et. al., 1988; Spohr et. al., 1993).

In summary, thousands of individuals with FAS have been identified and thousands of laboratory, clinical and population-based studies have been conducted. While these studies have greatly advanced our understanding of alcohol's teratogenic potential, advancements in the clinical and public health arenas are less impressive. To date, we still cannot derive an accurate estimate of the prevalence of FAS (Floyd et. al., 1994) nor can we document success in preventing FAS. Advancements in these two arenas are contingent upon physicians making accurate diagnoses. Accurate diagnoses require specific and objective case definitions that document the full range of outcomes associated with prenatal alcohol exposure. These definitions should be continually honed to incorporate the latest technological advances (e.g., magnetic resonance spectroscopy and functional MRI, digital image analysis, etc.) and should be guided by more sophisticated, multivariate, analytic approaches to pattern recognition.

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Application of the fetal alcohol syndrome facial photographic screening tool in a foster care population

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We determined the prevalence of fetal alcohol syndrome (FAS) in a foster care population and evaluated the performance of the FAS Facial Photographic Screening Tool. All children enrolled in a Washington State Foster Care Passport Program were screened for three conditions: (1) the FAS facial phenotype from a photograph, (2) evidence of brain damage with prenatal alcohol exposure from their Health and Education passport, and/or (3) other syndromes identifiable from a facial photograph. Screen-positives received diagnostic evaluations at a FAS Diagnostic and Prevention Network clinic. The prevalence of FAS in this foster care population was 10 to 15/1000, or 10 to 15 times greater than in the general population. The screening tool performed with 100% sensitivity, 99.8% specificity, 85.7% predictive value positive, and 100% predictive value negative. We conclude that the foster care population is a high-risk population for FAS. The screening tool performed with very high accuracy and could be used to track FAS prevalence over time in foster care to accurately assess the effectiveness of primary prevention efforts. (J Pediatr 2002;141:712-7)

Fetal alcohol syndrome (FAS), a permanent birth defect caused by maternal consumption of alcohol during pregnancy, is characterized by growth deficiency, central nervous system dysfunction, and a unique cluster of minor facial anomalies.[1,2] FAS is the leading known cause of mental retardation in the Western world[3] and is entirely preventable.

Primary prevention of FAS and prevention of secondary disabilities (eg, school/job failure, depression, trouble with the law) among persons with FAS are paramount. With the development of the FAS Facial Photographic Screening Tool,[1,4] the creation of the FAS 4-Digit Diagnostic Code[2,5,6] and the establishment of the Washington State FAS Diagnostic and Prevention Network (FAS DPN) of clinics,[7,8] FAS screening, diagnosis and prevention are now being effectively and efficiently conducted in Washington State.

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Targeting FAS prevention efforts to high-risk populations is an efficient and effective use of limited resources. Children in foster care serve as an ideal population to target. First, the risk of FAS in this population is likely to be high; as much as 75% of children in foster care have a family history of mental illness or drug or alcohol abuse.[9] Foster children comprised 2 to 5 times the normative percent of children below the 5th percentile for height and weight.[9,10] Developmental disabilities and mental health diagnoses are also disproportionately prevalent in foster children.[9,11] Second, early diagnosis helps reduce the risk of secondary disabilities.[12] Third, if a child's disabilities are fully known and disclosed at the time of placement, foster care systems will be able to establish more appropriate placements, foster/adoptive parents will be better prepared to meet their child's needs and the children are less likely to experience multiple failed placements. Finally, the population is readily accessible and thoroughly tracked.

95% CI	95% Confidence intervals
DCFS	Division of Children and Family Services
DPN	Diagnostic and Prevention Network
DSHS	Department of Social and Health Services
EPSDT	Early, periodic screening, diagnosis, and treatment
FAE	Fetal alcohol effect
FAS	Fetal alcohol syndrome
FCPP	Foster Care Passport Program
OFC	Occipital frontal circumference
PHN	Public health nurse

The primary objectives of this project were to: (1) screen all eligible children

in out-of-home care, enrolled in the Region 4 (King County) Foster Care Passport Program (FCPP), for the FAS facial phenotype, structural or neurologic evidence of brain damage with confirmed prenatal alcohol exposure, and/or other syndromes identifiable from a facial photograph; (2) provide all children who screen positive with comprehensive diagnostic evaluations and treatment plans through the FAS DPN of clinics; (3) determine the prevalence of FAS in this foster care population; and (4) evaluate the performance of the FAS Facial Photographic Screening Tool in a population-based sample.

METHODS

This FAS screening was a collaborative effort between the University of Washington FAS DPN, the Washington State Department of Social and Health Services (DSHS), Children's Administration, Division of Children and Family Services (DCFS), Region 4, and Public Health–Seattle and King County.

Subjects

All children who were legally dependent with the state of Washington and enrolled in the Region 4 FCPP on or after March 1, 1999 in King County, Washington, were eligible to participate in this screening. To be enrolled in the FCPP, a child had to be: (1) legally supervised by DCFS; (2) 0 to 12 years of age at the time of enrollment, but were able to remain in the program after their 12th birthday; (3) dependent; and (4) in out-of-home placement. Throughout this report, the term "foster care" will refer to children in out-of-home care that includes children in foster care or in the care of their relatives. Up to 500 children enter this FCPP annually.

To maximize the efficiency of the FAS Screening program, the screening was incorporated into an already established state program, the FCPP. The FCPP uses information regarding services already provided to children who receive Medicaid-covered health services, such as early, periodic screening, diagnosis, and treatment (EPSDT) examinations, as well as other health care information, to provide a comprehensive health picture of each enrolled child. Children who remain in out-of-home placement for 90 consecutive days are automatically referred through the DSHS information system to the FCPP. A public health nurse (PHN) and a health program assistant work as a team to seek out and gather all available health history information (from birth to present) for each child enrolled in the program. The PHN interprets and enters all information into a computerized Health and Education database. A shortened summary (a Health and Education "passport") is provided with health recommendations to the social worker and the foster parent to share with the child's health care provider(s). Each child's passport is updated every 6 months. By nesting the FAS screening into an already existing program, the screening program had access to a computer-generated eligibility list, current names and addresses of all foster parents and caseworkers, and a concise summary of the child's health/educational history. When the screening was complete, the child's screening and diagnostic outcomes, as well as their electronic facial photograph, were entered into the Health and Education Database and case file. This provided immediate and broad access to this information for future medical/social service care and placement decisions. This screening activity was approved by the Human Research Review Boards of Washington State and the University of Washington.

Enrollment

The FCPP identified all eligible children, obtained written consent from the child's legal guardian (DCFS social worker), sent the child's foster parents a letter that explained the purpose and process of the FAS screening, and sent the FAS DPN the list of all newly eligible, consented children, weekly. The FAS DPN scheduler called each foster parent to schedule a photography appointment with one of the two FAS DPN photographers.

Facial Photograph and Head Circumference

Two University of Washington students were trained to take three standardized facial photographs (frontal, ¾ view and lateral) by using a handheld, 3-megapixel, digital camera. The guidelines of Astley and Clarren[16] and the FAS Tutor CD ROM[17] were followed. The photographers were also shown how to measure the child's head circumference (occipital frontal circumference (OFC). During a 20-minute photography session at the child's foster home, the photographer took the standardized photographs, one casual portrait photograph (to give to the child as a way of thanking them and assuring them they were a fine looking child) and the OFC. The photographers transferred the photographic images and OFC measures to the University of Washington FAS DPN image analysis laboratory weekly.

A small proportion (20%) of the children had foster placements with relatives who lived outside King County or outside Washington State. These families were sent a disposable camera with a one-page pictorial instruction sheet for how to take the three standardized photographs. A stamped, addressed envelope was enclosed for them to return the camera. Parents were not requested to measure their child's OFC. We relied on OFC measures in the child's passport, when available. The FAS DPN scanned the photos to generate electronic image files. On occasion, a second camera had to be sent to the family because the lower resolution of the photos from the disposable camera were not of sufficient quality to provide an accurate screen.

Review of the Foster Care Health and Education Passport

All passports were reviewed by S. J. A. The passport was used to screen for structural or neurologic evidence of

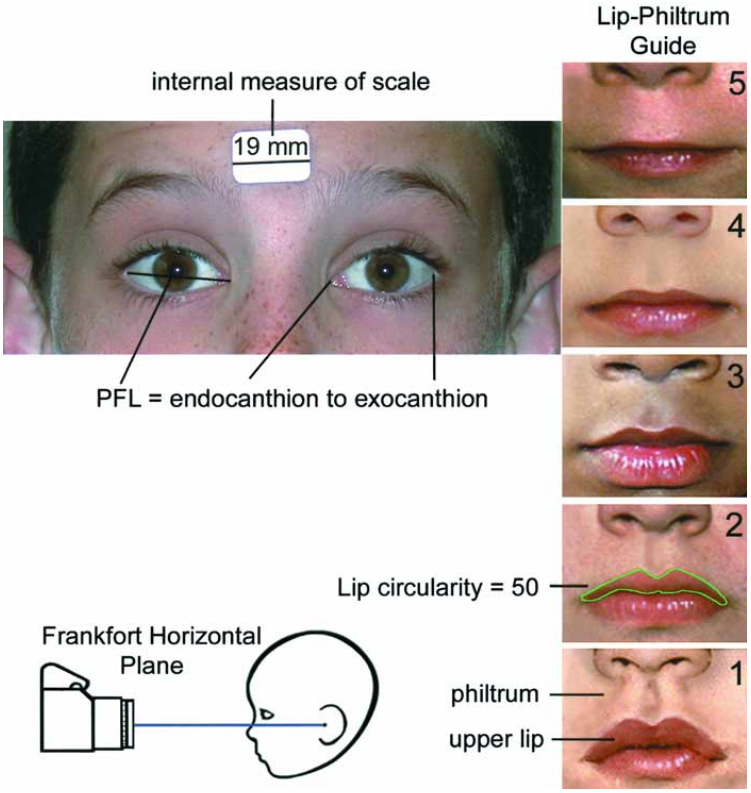

Figure. A standardized, digital, frontal facial photograph is taken while aligning the center of the camera lens in the patient's Frankfort horizontal plane (a plane extending from the patient's upper margin of the external auditory meatus [porion] through the lowest margin of the lower bony orbital rim [orbitale]). An internal measure of scale *(19 mm paper sticker)* is placed between the patient's eyebrows to serve as a ruler or internal measure of scale in the photo. Three facial features are measured: (1) the palpebral fissure length *(PFL)* or distance between the endocanthion and exocanthion landmarks, (2) philtrum smoothness, and (3) upper lip thinness. The PFL is converted to a *Z* score (or number of SD above or below the norm) by using appropriate normal anthropometric tables.[19] The philtrum is ranked using the 5-point Likert scale depicted on the Lip-Philtrum Guide. The upper lip is first outlined with the computer mouse to generate a quantitative measure of thinness called circularity (perimeter^2/area). It is then ranked on the 5-point Likert scale depicted on the Lip-Philtrum Guide by using circularity as a guide. The circularity of each upper lip pictured on the Lip-Philtrum Guide is: Rank 5 = 178, Rank 4 = 85, Rank 3 = 65, Rank 2 = 50, and Rank 1 = 35.

brain damage (seizures, microcephaly, abnormal brain magnetic resonance imaging/computed tomography/ positron emission tomography scans, neurologic disorders) and documentation of prenatal alcohol exposure, and to generate a clinical profile of the screened population. The clinical profile served to describe the study population and assess the performance of the photographic screening tool. When screening a population-based sample, one rarely gets the opportunity to assess the screen-negative subjects to confirm they were truly negative. The passports provided an invaluable opportunity to review the medical histories and prenatal exposures of all screen-negative children to determine if any of the three remaining key diagnostic features of FAS (growth deficiency, brain dysfunction, and prenatal alcohol exposure) were present in a child.

Facial Photographic Assessment

Image analysis software[18] was used to measure the magnitude of expression of the FAS facial phenotype (short palpebral fissure lengths, smooth philtrum, and thin upper lip) from the digital images (Figure). Briefly, the image is presented on a computer monitor, the three facial features are measured, and the magnitude of expression of the FAS facial phenotype is classified into one of 4 case-defined categories; normal, mild, moderate, or severe.[16] The photographs were also reviewed by a dysmorphologist for the presence of other minor and/or major anomalies that may or may not be part of another syndrome. Assessment of the photographs took approximately 10 minutes per child.

Screen-Positive Definition for FAS

A child was screened positive for FAS if all three of the following features were present in their facial photograph: (1) palpebral fissure lengths were >2 SD below the mean,[19] (2) the philtrum was smooth (Likert rank 4 or 5 on the 5-point Lip-Philtrum Guide), and (3) the vermilion border of the upper lip was thin (Likert rank 4 or 5 on the 5-point Lip-Philtrum Guide [circularity ≥75]) (Figure).[4,16] Confirmation of prenatal alcohol exposure was not required at the time of the screening because this facial phenotype is so highly specific to prenatal alcohol exposure.[4] Confirmation was sought at the time of diagnosis. This case-definition of the facial phenotype was derived analytically by Astley and Clarren[4] and matches the original 1979 definition by Smith.[20]

Screen Positive Definition for Structural or Neurologic Evidence of Brain Damage with Prenatal Alcohol Exposure

A screening tool to accurately identify persons at risk for fetal alcohol effects (FAE) does not exist because cognitive/behavioral dysfunction associated with prenatal alcohol exposure is not sufficiently specific to prenatal alcohol exposure to clinically label the outcome as a specific FAE. It is for that reason that FAE is not a medical-

ly recognized diagnosis.[21,22] The number of persons with brain damage caused by prenatal alcohol exposure who do not have FAS far exceeds the number of persons with FAS. Current medical technology simply cannot confirm that a patient's brain damage/dysfunction was caused by their prenatal alcohol exposure when the patient does not have the FAS facial phenotype. But identification and treatment of persons with brain damage does not require confirmation of etiology. Prenatal alcohol exposure and structural/neurologic evidence of brain damage are clear risk factors for brain damage/dysfunction. If prenatal alcohol exposure *and* structural or neurologic evidence of brain damage (microcephaly, seizures of unknown origin, abnormal brain image) were present, the child was screened positive for static encephalopathy/alcohol exposed. Confirmation of prenatal alcohol exposure at the time of the screening was required because a secondary goal of this study was to identify birth mothers at high risk of exposing future children to damaging levels of prenatal alcohol exposure.

Procedure Followed When a Child Screened Negative

An FAS screen-negative medical note and the child's portrait photographs were sent to the FCPP and the foster parents. The medical note included the statement that a child could still have problems related to prenatal alcohol exposure that will not show up in a facial photograph; thus if they had concerns about the child's growth or development, they should talk with the child's health care provider.

Procedure Followed When a Child Screened Positive for FAS and/or Brain Damage/Alcohol Exposed

When a child screened positive for either FAS or structural/neurologic evidence of brain damage with confirmed prenatal alcohol exposure, the following documents were sent to the FCPP: (1) a standardized screen-positive medical note, (2) an FAS DPN clinic registration packet, and (3) copies of the child's portrait photograph. The FCPP notified the social worker, entered the screen-positive results in the Health and Education database, updated the passport and health recommendations, completed the FAS DPN registration packet, and provided the social worker with an updated passport packet for the DCFS file, along with the FAS DPN registration packet. The foster parents were initially informed of the screen-positive outcome by the FCPP PHN. The foster child, accompanied by his/ her foster parents and caseworker, was subsequently scheduled for a diagnostic evaluation at the FAS DPN clinic where he/she received a comprehensive diagnostic evaluation and treatment plan by the multidisciplinary team using the 4-Digit Diagnostic Code.[2,23]

Procedure Followed When a Child Screened Positive for Other Facial Anomalies/Syndromes

When the dysmorphologist identified other minor/major craniofacial anomalies that were either consistent with another syndrome or warranted further follow-up, the child's medical record was reviewed and the child was referred to a clinical geneticist or craniofacial clinic, if appropriate. Information, in the form of a medical note, was sent from the FAS DPN to the FCPP. All information received by the FCPP was entered into the database. Updated passports and health recommendations were supplied to the foster family as well as the assigned social worker, including any recommendations for further evaluation.

Data Analysis

The prevalence of FAS (number of children with FAS/number of children screened) with 95% confidence intervals (95% CI) was computed. A binomial test was used to determine if the observed prevalence of FAS in this foster population was significantly different from the estimated prevalence of 1 to 3 per 1000 live births reported in the general population.[24]

RESULTS

Sociodemographics and Participation Rate

In this ongoing screening activity, 793 children were eligible to participate between March of 1999 and September of 2001. Of these 793 children, 592 have been screened to date, 8 had already received an FAS diagnostic evaluation before the screening program, 129 are in the process of being screened, 10 chose not to participate, and 54 left foster care before completing the screening. The diagnostic outcomes of the 8 children were combined with the screening outcomes of the 592 children to serve as the study population of 600 children for this first screening program assessment. The 600 children were on average 5.8 ± 4.1 SD years of age at the time they were screened, 48% were female, 48% were white, 32% were black, 12% were Native American, 15% had documented prenatal alcohol exposure, and 32% had documented prenatal drug exposure. The 64 children who did not participate in the screening were nearly identical in profile to the 600 who did participate. The participation rate to date is 98.6%. Only 10 families of 739 chose not to participate.

FAS Screen-Positive Outcomes

Of the first 600 children screened to date, 10 screened positive for FAS. They were 5.5 ± 3.1 years of age (range, 1.1-11.4 years), 30% female, 40% white, 20% black, and 10% Native American. Nine of the children had confirmed prenatal alcohol exposure; one, still pending review, has a family history of alcohol abuse. Four of the 10 children who screened positive for FAS had microcephaly and only one was significantly growth deficient

(height and weight <3rd percentile). Six had documented prenatal exposure to illicit drugs. Diagnostic evaluations have been conducted on 7 of the 10 children to date in this ongoing screening. Six of the seven received a diagnosis of FAS. The 7th child had the full facial features, attention deficit–hyperactivity disorder, poor adaptation skills, borderline concerns in visual-motor integration and soft neurologic signs, significant impairment in academics, and prenatal alcohol exposure. This profile fell just short of a full diagnosis of FAS using the 4-Digit Diagnostic Code. He received a diagnosis of sentinel physical findings/neurobehavioral disorder/alcohol exposed. None of these 7 children had been previously diagnosed with FAS. A one-year old child who screened positive for the FAS facial phenotype also had Down syndrome. This child was subsequently diagnosed with FAS (4-Digit Diagnostic Code 4444), presenting with height and weight <1% when plotted on a growth chart for children with Down syndrome, microcephaly and daily exposure to alcohol throughout gestation.

Estimated Prevalence of FAS

Due to the ongoing nature of this screening, 3 of 10 screen-positive children have not yet received diagnostic evaluations. Thus, the prevalence of FAS will fall between the following minimum and maximum estimates. If none of the three remaining children receive a diagnosis of FAS, the prevalence of FAS in this foster care population will be 6 of 600 or 10 of 1000 (95% CI, 5-22 per 1000). If all three receive a diagnosis of FAS, the prevalence of FAS will be 9 of 600 or 15 of 1000 (95% CI, 8-28 per 1000). Both of these FAS prevalence estimates are statistically significantly greater (binomial test: P values < .001) than the FAS prevalence estimate of 1 to 3 per 1000 live births in the general population reported by the National Institute of Alcohol Abuse and Alcoholism.[24]

Screen Positive for Structural or Neurologic Evidence of Brain Damage with Prenatal Alcohol Exposure, But Did Not Have the FAS Facial Phenotype

Fifteen (2.5%) of the 600 children screened positive for structural or neurologic evidence of brain damage with prenatal alcohol exposure, but did not have the FAS facial phenotype. They were 5.0 ± 3.6 years of age (range, 0.7-13.3 years), 47% female, 40% white, and 20% black. Three had seizure disorders of unknown origin and 12 had microcephaly. Nine of the 15 children have been diagnosed to date. All 15 currently meet the FAS DPN diagnostic criteria for static encephalopathy/alcohol exposed. Four of the 9 currently diagnosed also have growth deficiency.

Other Anomalies/Syndromes

Eight of the 600 (1.3%) children presented with other clusters of minor and/or major facial anomalies (including two with Down syndrome). They were 38% white, 38% black, 24% Native American, 63% female, and ranged in age from 0.6 to 10.1 years. All but two of the children had been previously identified and were receiving appropriate care. Two of the 8 had prenatal alcohol exposure, including one of the two with Down syndrome. The FAS facial analysis system clearly differentiated the two children with Down syndrome who did and did not have FAS.

Performance of the FAS Facial Photographic Screening Tool

Based on the seven screen-positive children with completed diagnostic evaluations and the 590 screen-negative children, the predictive value positive for the FAS photographic screening tool is 6 of 7 or 85.7%.[25] The predictive value negative for the screening tool is 590 of 590 or 100%. The sensitivity of the screening tool in this population-based sample is 6 of 6 or 100%. The specificity of the screening tool in this population-based sample is 590 of 591 or 99.8%. The accuracy of the tool is 596 of 597 or 99.8%. Unlike most population-based screening programs, this program had the unique ability to confirm that the 590 screen-negatives were true negatives. This confirmation was possible because the tool used to screen for the FAS facial phenotype is the same tool used to diagnose the facial phenotype in clinic.

DISCUSSION

This FAS screening program confirmed that foster care is a high-risk population for FAS, that screening for FAS in this population can be done accurately, efficiently, and with direct benefit to the children and their families, and that the FAS DPN Facial Photographic Screening Tool performs with high accuracy in a population-based sample.

During the course of this screening activity, several additional observations were made that further support the merits of FAS screening in a network of affiliated clinics. First, there was an unexpected opportunity to demonstrate that screening can lead to both primary and secondary prevention intervention for FAS. One child who screened positive for FAS returned to the care of their birth mother before the diagnostic evaluation. The birth mother willingly accompanied her child to the diagnostic appointment and received support and treatment referrals tailored to meet her needs as well as those of her child. Second, if a child's disabilities are fully known and disclosed at the time of placement, the risk of multiple failed placements could be reduced. This was observed in two children who screened positive for FAS, both of whom had multiple failed placements before diagnosis and have maintained a single successful placement since receipt of their diagnoses. Third, although the primary focus of this screening was on FAS, this activity led to increased awareness and understanding by foster parents and caseworkers of the risks of prenatal al-

cohol exposure among all children, not just children with the FAS facial features. This, in turn, led to an increase in appropriate referrals of children to the FAS DPN clinics who had prenatal alcohol exposure, cognitive/behavioral problems, but screened negative for FAS. Finally, the value of a national network of FAS DPN clinics was demonstrated when one child who screened positive for FAS lived 1600 miles outside Washington State, but was readily diagnosed by an affiliated FAS DPN multidisciplinary clinical team just a few miles from where the child lived.

The next step for the FAS DPN screening program will be to track the annual change in prevalence of FAS in this foster care population to assess the effectiveness of community FAS primary prevention efforts. Statewide expansion of the screening is also being explored. The screening program was both cost-effective and time efficient in large part because of nesting it into an already existing state-run program. Expansion of the screening program will be facilitated by FAS Facial Photographic Analysis software[18] developed by the FAS DPN. The software will allow the user to measure the key facial features from digital photographs and generate a hard copy or electronic outcome report within minutes.

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Fetal alcohol syndrome prevention in Washington State: evidence of success

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Summary

Fetal alcohol syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. It is characterised by growth deficiency, central nervous system damage/dysfunction, and a unique cluster of minor facial anomalies. To assess the effectiveness of fetal alcohol syndrome prevention efforts, one must be able to estimate accurately the prevalence of fetal alcohol syndrome over time in population-based samples. With the establishment of the Washington State Fetal Alcohol Syndrome Diagnostic and Prevention Network of clinics, the development of the Fetal Alcohol Syndrome Facial Photographic Analysis Software, the creation of the Fetal Alcohol Spectrum Disorders (FASD) 4-Digit Diagnostic Code, the establishment of the Foster Care Fetal Alcohol Syndrome Screening Program, and the collection of Pregnancy Risk Assessment Management System data on maternal use of alcohol during pregnancy, the tools, methods and infrastructure for assessing the effectiveness of fetal alcohol syndrome primary prevention efforts in Washington State are in place. A cross-sectional study was conducted to determine whether the prevalence of fetal alcohol syndrome among children in a foster care population, born between 1993 and 1998, decreased with the documented decrease in prevalence of maternal use of alcohol during pregnancy from 1993 and 1998 in Washington State.

The prevalence of maternal drinking during pregnancy in Washington State declined significantly ($P < 0.001$) from 1993 to 1998 as did the prevalence of fetal alcohol syndrome among foster children born 1993–98 ($P < 0.03$). These observations support the likelihood that fetal alcohol syndrome prevention efforts in Washington State are working successfully.

Introduction

Fetal alcohol syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. It is characterised by growth deficiency, central nervous system (CNS) damage/dysfunction, and a unique cluster of minor facial anomalies.[1,2] It is also the leading known cause of mental retardation/developmental disabilities in the western world[3] and is entirely preventable. The prevalence of FAS is estimated to be 1–3 per 1000 live births[4] in the US general population, but has been documented to be as high as 15 per 1000 in some high-risk populations.[5]

To prevent FAS, maternal alcohol consumption during pregnancy must be avoided. Prevention efforts span a broad continuum from public health education and policy[6–13] to direct intervention targeted to high-risk women.[10] To assess the effectiveness of FAS prevention efforts, one must be able to estimate accurately, consistently and efficiently the prevalence of FAS over time in population-based samples. Accurate estimates of prevalence, in turn, require accurate diagnostic methods. With the establishment/development of the Washington State FAS Diagnostic and Prevention Network (FAS DPN) of clinics in 1993,[14–17] the computerised FAS Facial Photographic Analysis Software in 1995,[18–20] the FASD 4-Digit Diagnostic Code in 1997,[2,21,22] the Foster Care FAS Screening Program in 1999,[5] and ongoing collection of Pregnancy Risk Assessment Monitoring System (PRAMS) data by

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Washington State since 1993,[23–25] the methods and infrastructure for assessing the effectiveness of FAS primary prevention efforts through FAS screening, diagnosis and surveillance are now in place in Washington State.

The purpose of this cross-sectional study was to determine if the prevalence of FAS among children in a foster care population, born between 1993 and 1998, decreased with the documented decrease in prevalence of maternal use of alcohol during pregnancy from 1993 to 1998 in Washington State.

Methods

Prevention efforts in Washington State

Fetal alcohol spectrum disorder was identified at the University of Washington in 1970 by Ulleland and Smith[1] spawning two major clinical/research programmes, the FAS DPN[14] and the Fetal Alcohol and Drug Unit,[26] which have made significant contributions over the past three decades to screening, diagnosis, education and prevention of FASD. Washington State prevention efforts have reflected the full continuum of strategies from public health education and training[6,8,11,12,27] to direct intervention with high-risk women.[28–30] Although prevention efforts have been ongoing since the early 1970s, a substantial increase in effort began in 1992 with the implementation of FAS prevention projects sponsored by the Centers for Disease Control,[16,17,31,32] establishment of the Parent–Child Assistance Program,[29] and a legislative mandate in 1995[33] for statewide expansion of the FAS DPN and establishment of the FAS Interagency Work Group to ensure coordination of efforts across key state agencies including family advocacy groups.[34]

Surveillance of maternal drinking during pregnancy in Washington State

PRAMS is a CDC-sponsored, ongoing, population-based surveillance system designed to monitor self-reported maternal behaviours that occur before, during and after pregnancy.[23–25] Washington State is one of 31 states participating in PRAMS and the Washington State Department of Health has collected PRAMS data since June 1993. Each month, 1 in 40 live births are randomly selected from the Washington State birth certificates. Over-sampling by race other than Caucasian is conducted to increase the reliability of estimates for these racial groups. The data are then weighted to reflect the true racial profile of the state. At two to 6 months postpartum, the sampled mothers ($n = 2000$/year) are sent an explanatory letter and a self-administered PRAMS questionnaire. Non-respondents are sent a second questionnaire by mail and then multiple attempts to follow up are conducted by telephone. In the first year of data collection (1993), data were collected over 9 rather than 12 months with a response rate of 61%. For all other years, data were collected over 12 months with an average response rate of 70%.

The PRAMS questionnaire currently includes 66 questions (52 core questions and 14 state-specific questions). The core questions address obstetric history and risk factors, maternal feelings about timing of pregnancy, maternal economic status, birth control, prenatal care, folic acid awareness, prenatal behaviours and experiences (cigarette smoking, alcohol use, psychosocial stress during the 12 months prior to delivery, and physical abuse before and during pregnancy), prenatal hospitalisation, labour and delivery, and infant health. Two core questions documenting alcohol use include: 'During the 3 months before you got pregnant, how many alcoholic drinks did you have in an average week?' and 'During the last 3 months of your pregnancy, how many alcoholic drinks did you have in an average week?' Reported use of alcohol 3 months prior to pregnancy is deemed the most accurate measure of early pregnancy use because women often do not know they are pregnant until the second month and typically do not change their drinking patterns until they know they are pregnant.[35,36] A drink was defined as: one glass of wine, one wine cooler, one can or bottle of beer, one shot of liquor or one mixed drink. Women were asked to select from the following choices: I didn't drink then; 1–3 drinks per week, 4–6 drinks per week, 7–13 drinks per week, 14 or more drinks per week; I don't know.

To date, prevalence estimates for maternal use of alcohol 3 months prior to pregnancy and during the third trimester of pregnancy are available from 1993 to 1998 in Washington State from 12 388 women.[23–25]

Prevalence of FAS in a Washington State foster care population

In 1999, the FAS DPN implemented FAS screening and diagnosis of all children entering the Foster Care Passport Program (FCPP) in King County, Washington using the FAS Facial Photographic Analysis Software[5,19,20] and the FAS 4-Digit Diagnostic Code.[2,21]

Details on the performance of the screening tool and the prevalence of FAS among the first 600 children screened have been published previously.[5] Briefly, all children, who were legally dependent with the State of Washington and enrolled in the Region 4 FCPP on or after 1 March 1999 in King County, Washington were eligible to participate in the screening. To be enrolled in the FCPP, a child had to be: (a) legally supervised by the Department of Social and Family Services; (b) 0–12 years of age at the time of enrolment, but may remain in the programme after their 12th birthday; (c) dependent and (d) in out-of-home placement.

To screen for FAS, a photographer from the FAS DPN was sent to the home of the foster child to take standardised, digital facial photographs with an internal measure of scale placed in the photo. A child screened positive for FAS if they had all three of the following facial features: palpebral fissure lengths two or more standard deviations below the mean, a smooth philtrum (Likert rank 4 or 5 on the 5-point Lip-Philtrum Guide) and a thin upper lip (Likert rank 4 or 5 on the 5-point Lip-Philtrum Guide) (Fig. 1).[18–21] This case-definition for the FAS facial phenotype was derived analytically by Astley and Clarren,[18] matches the original 1979 definition by Smith,[37] and has been found to be highly sensitive and specific to FAS.[18] Image analysis software[20] developed by the FAS DPN was used to measure the magnitude of expression of the FAS facial phenotype from the digital images. This procedure is described in detail by Astley and Clarren[19] and demonstrated in a CD-ROM.[22]

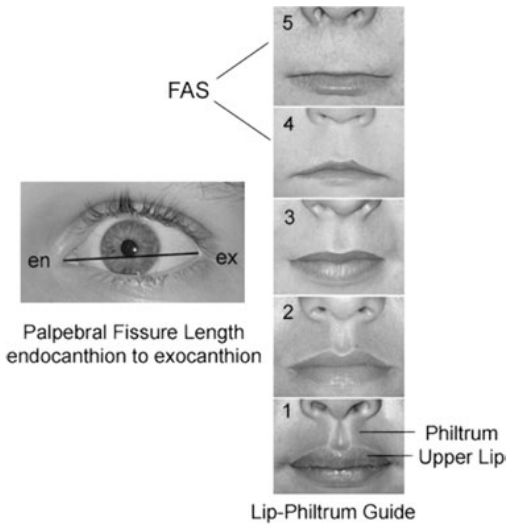

Figure 1. The three facial features of FAS include: (a) palpebral fissure lengths (the distance between the endocanthion and exocanthion landmarks) two or more S.D.s below the mean; (b) philtrum smoothness = Rank 4 or 5 on Lip-Philtrum Guide; and (c) upper lip thinness = Rank 4 or 5 on Lip-Philtrum Guide.

All children who screened positive for the FAS facial phenotype were scheduled for a diagnostic evaluation at the FAS DPN clinic where they received a comprehensive diagnostic evaluation and treatment plan by the interdisciplinary team using the 4-Digit Diagnostic Code.[2,15,21] The 4-Digit Diagnostic Code is an objective, case-defined method for diagnosing the full spectrum of outcomes associated with prenatal alcohol exposure. It was developed to increase diagnostic accuracy and reproducibility. The screening activity was approved by the Human Research Review Boards of Washington State and the University of Washington. This ongoing screening activity has demonstrated that: (1) the prevalence of FAS in this foster care population is 10–15 per 1000, (2) the screening tool performs with 100% sensitivity and 99% specificity in this population-based sample, and (3) screening can be accomplished on a near complete (98%) sample of this population.[5] The population screened ranged in age from 3 months to 15 years, was 48% female and had a racial distribution of 48% Caucasian, 32% African American and 12% Native American. The subset of five children diagnosed with FAS ranged in age from 1 to 11 years, three were female, two were Caucasian and three were African American.

Since Washington State PRAMS data documented a significant decline in maternal use of alcohol during pregnancy from 1993 to 1998, one might expect to see a decrease in the prevalence of FAS among children born in those years (1993–98). The Foster Care FAS Screening/Diagnostic Program provided a unique opportunity to assess change in prevalence of FAS over time in a high-risk population-based sample. The first step was to identify all children born from 1993 to 1998 ($n = 264$) among the first 600 children who participated in the screening programme. This was necessary because maternal use of alcohol during pregnancy from 1993 to 1998 could only affect children born in those years.

The proportion of children who were diagnosed with FAS within each of these six birth cohorts was computed. The prevalence of FAS was computed by birth cohort rather than by year of entry into foster care because the former would be far more sensitive in

documenting change. While a reduction in maternal drinking over time should result in a decrease in the prevalence of FAS among children entering foster care in each successive year, the decrease from year to year would be quite small because children entering foster care in any single year will range in age from birth up to 18 years old. For example, children entering foster care through the Foster Care Passport Program in the year 2000 will have been born across 12 different birth cohorts from 1988 to 2000. The prevalence of FAS among children entering foster care in 2000 would be influenced by the drinking patterns of their mothers from 1988 to 2000. Any reduction in drinking in the late 90s could be masked by the higher prevalence of drinking in the early 90s. Thus, to document the impact of maternal drinking on risk of FAS from year to year, the prevalence of FAS needs to be based on the year the child was born, not the year the child entered foster care.

Analysis

The chi-square test for linear trends was used to assess the change in prevalence of maternal drinking and change in prevalence of FAS from 1993 to 1998. Pearson and Spearman ρ correlation coefficients were computed to assess the correlation between prevalence of maternal drinking in early and late pregnancy and prevalence of FAS. Pearson and Spearman ρ were used when data were normally and not normally distributed respectively.

Results

Change in prevalence of alcohol use over time

Washington State PRAMS data show that the prevalence of maternal alcohol use 3 months prior to pregnancy and during the third trimester declined significantly (chi-square = 66.9, $P < 0.001$ and chi-square = 101.3, $P < 0.001$, respectively) from 1993 to 1998, exceeding the Healthy People 2010 objective of 6%[38] (Table 1, Fig. 2). This decline is most striking among the women reporting the highest levels of use (>14 drinks/week) in early pregnancy (chi-square = 64.5, $P < 0.0001$).

Change in prevalence of FAS over time

Of the first 600 children who participated in the foster care FAS Screening Program,[5] 264 were born from 1993 to 1998. Five of these 264 children screened positive and were diagnosed with FAS.[5] A diagnosis of FAS required all of the following to be present: height and weight at or below the 10th percentile; all three FAS facial features as described in Fig. 1; evidence of significant structural, neurological or functional CNS damage and a confirmed history of prenatal alcohol exposure.[2] The prevalence of FAS among these 264 foster children declined significantly (chi-square = 4.7, $P = 0.03$) across each birth cohort from 1993 to 1998. (Table 2, Fig. 2).

Table 1. Decline in the prevalence of women reporting alcohol use 3 months prior to pregnancy and in the third trimester of pregnancy in Washington State from 1993 to 1998[23–25]

		Average drinks per week					
Year	*N*	<1	1–3	4–6	7–13	>14	>0
Three months before pregnancy ($n = 12\,063$)							
1993	1254	50.1	29.0	11.9	4.2	4.9[a]	51.5[a]
1994	2430	51.3	29.0	10.7	5.3	3.7	57.3
1995	1985	55.5	26.6	12.4	3.5	2.0	49.8
1996	2069	51.8	29.9	12.1	3.4	2.8	49.6
1997	2098	51.7	28.4	11.7	6.3	2.0	46.5
1998	2227	55.4	27.9	12.4	3.6	0.7	44.3
Third trimester ($n = 12\,198$)							
1993[c]	1293	72.8	21.3	0.2	3.2	2.5	14.6[b]
1994	2430	75.0	20.1	2.0	2.8	0.1	7.8
1995	2017	79.6	17.5	2.5	0.1	0.4	8.2
1996	2105	83.7	12.8	3.4	0.0	0.1	8.3
1997	2116	88.2	8.3	3.2	0.0	0.3	6.2
1998	2237	80.6	18.3	0.9	0.1	0.2	3.9

[a]Three months before pregnancy: test for linear trend from 1993 to 1998. Drinking >0 drinks/week: chi-square = 66.9, $P < 0.0001$. Drinking >14 drinks/week: chi-square = 64.5, $P < 0.0001$.
[b]Third trimester of pregnancy: test for linear trend from 1993 to 1998. Drinking >0 drinks/week: chi-square = 101.3, $P \leq 0.001$. The Healthy People 2010 objective is to reduce the prevalence of drinking during pregnancy to 6%.[38]
[c]Data were collected over 9 months in this first year with a response rate of 61%. For all other years, data were collected over 12 months with an average response rate of 70%.

Correlation between maternal drinking and FAS prevalence

The prevalence of alcohol use during pregnancy from 1993 to 1998 in this statewide sample of women was compared with the prevalence of FAS among children born between 1993 and 1998 in this King County foster care population. Despite the cross-sectional nature

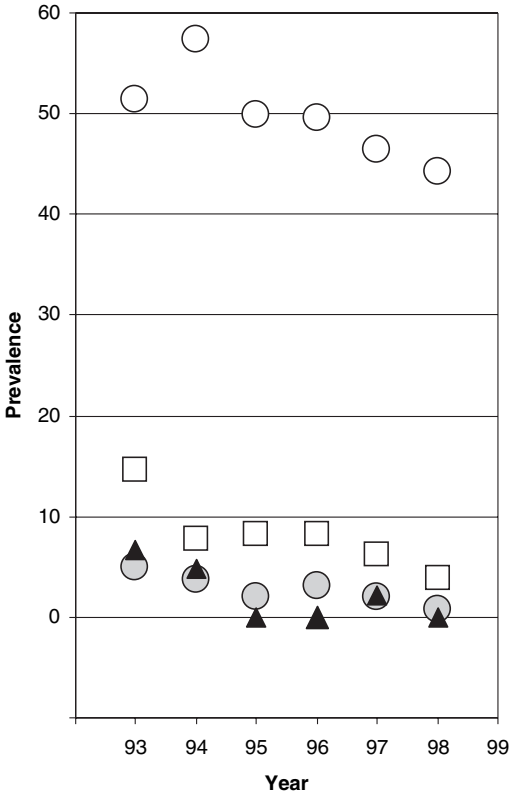

Figure 2. Decline in the prevalence of alcohol use by women in Washington State. (○) Any level of alcohol use 3 months prior to pregnancy; (□) Any level of alcohol use in the third trimester of pregnancy; (◍) Heavy alcohol use (>14 drinks/week) 3 months prior to pregnancy from 1993 to 1998;[23–25] (▲) Prevalence of FAS among children in the King County Foster Care Passport Program born from 1993 to 1998.[5]

of these data, remarkably strong correlations were observed that increased in strength as the risk in timing and level of maternal alcohol use increased. When the analysis focused on the timing of alcohol use, the decline in FAS was more strongly correlated with the decline in maternal alcohol use in early pregnancy (Pearson Correlation Coefficient = 0.61, $P = 0.200$) than in late pregnancy (Spearman's $\rho = 0.33$, $P = 0.52$). This stronger correlation between FAS and early pregnancy exposure would be expected since (1) the FAS facial features are caused by alcohol exposure in the first 8 weeks of pregnancy and (2) the PRAMS question 'How much were you drinking in the third trimester?' would fail to identify a subset of women at high risk for bearing children with FAS (namely, women who did not drink in the third trimester, but did drink heavily in early pregnancy before they knew they were pregnant). When the analysis focused on both timing and level of alcohol use, the decline in FAS was most strongly and significantly correlated with the decline in prevalence of women reporting the highest-risk drinking pattern (>14 drinks/week in early pregnancy). The Pearson Correlation Coefficient was 0.86 ($P = 0.028$). The power to detect statistically significant correlations was limited by the number of years data were available ($n = 6$). This study had 80% power to detect correlation coefficients ≥0.85, at a two-tailed alpha level of 0.05.

Discussion

PRAMS data document a significant decline in the prevalence of maternal alcohol use during pregnancy from 1993 to 1998. The FAS DPN Screening/Diagnostic Program documents a significant decline in the prevalence of FAS among foster children born between 1993 and 1998. These observations support the likelihood that FAS prevention efforts in Washington State are working successfully. While this study was not designed to determine which prevention efforts were most effective, the prevention literature strongly supports that a comprehensive approach that utilises the entire spectrum of effort from public health education to targeted intervention has the greatest impact.[10,11]

Although the declines in maternal drinking and FAS observed in this study were statistically significant, these declines are based on very subtle annual reductions (each declining by just a few percentage points per year). Detection of subtle changes in FAS prevalence requires use of diagnostic and screening methods that are specifically case-defined so that they can be

Table 2. Decline in the prevalence of FAS among 264 children in the King County Foster Care Passport Program born from 1993 to 1998

Birth cohort	Number screened	FAS prevalence[a]	FAS *n*
1993	30	6.67%	2
1994	42	4.76%	2
1995	39	0.00%	0
1996	45	0.00%	0
1997	46	2.17%	1
1998	62	0.00%	0

[a]Chi-square test for linear trend from 1993 to 1998 = 4.7, $P = 0.03$.

accurately and reproducibly administered from year to year on a complete population-based sample. Typically, FAS surveillance activities to date have been population-based and rely on records-based data abstraction to generate prevalence estimates.[39–42] The FAS DPN screening, diagnostic and surveillance programme is unique because it integrates all three of these activities, capitalising on the inherent strengths of each. For example, the FAS DPN starts by screening all children in a foster care population with a FAS screening tool that performs with 100% sensitivity and 99.8% specificity. The FAS screening tool performs with the accuracy of a diagnostic tool because it is the diagnostic tool used to measure the FAS facial phenotype. The screening activity doubles as a highly effective surveillance activity because near-complete case ascertainment (98%) is achieved. High ascertainment is accomplished because the photographic screening tool can be practically administered and is targeted to a population that is (1) specifically defined, (2) readily tracked over time, and (3) motivated to participate because of the direct benefits. All children who screen positive receive a comprehensive diagnostic evaluation by a interdisciplinary team using the *same* diagnostic method (the 4-Digit Diagnostic Code).

At the time of diagnosis, the team reviews all medical, social service and educational records available on the child in addition to obtaining measures of growth, face, brain function and alcohol exposure through caregiver interview and direct clinical evaluation of the child. In contrast, a typical surveillance programme will rely on the passive chance that: (1) a child utilises the health care system; (2) a FAS diagnostic evaluation is conducted; (3) the surveillance programme obtains a copy of the relevant medical record(s); and (4) the record contains both accurate and sufficient information to confirm the child does or does not have FAS.

In a records-based approach to surveillance, all children will not have an equal chance of being correctly identified because the diagnostic methods used will vary from child to child and the accuracy of the data in the medical record cannot be confirmed as the child is never seen directly by the surveillance programme. This will limit the ability of the programme to track subtle changes in prevalence over time. In addition, surveillance programmes that rely on record abstraction often have to rely on proxy case definitions of FAS rather than the true clinical definition because the data needed to confirm a diagnosis of FAS is often not present in the medical or psychological records.[39] The inadequacy and variability of medical record documentation of FAS is well documented in the literature[40] and has been our experience in the FAS DPN clinic for the past 12 years.

Of the first 1390 patients evaluated in the FAS DPN clinic, 91 received a diagnosis of FAS using the 4-Digit Diagnostic Code. Although 60% of these 91 patients were over the age of 5 years at the time of diagnosis, only 8 had records documenting a previous evaluation and diagnosis of FAS. These 8 patients ranged in age from 1 to 24 years old. Of the 1299 patients that did not receive a diagnosis of FAS in the FAS DPN clinic, 24 had previously been diagnosed with FAS, but neither their medical records nor direct evaluations could substantiate the diagnosis. Similar observations were made among the children enrolled in the Foster Care FAS Screening/Diagnostic Program. All 10 children who screened positive for FAS among the first 600 children enrolled had no documentation of risk of FAS in their medical, school or psychological records even though the oldest was 11 years old and most had several inches of records. All 10 children would have been missed by a records-based approach to surveillance.

Another important and unique strength of the FAS DPN approach to surveillance is the potential for direct benefit to the child and their family. Typically, surveillance programmes have no direct contact with subjects and thus, provide no direct benefit to them. In contrast, the FAS DPN program, through its initial screening and diagnostic phases, provides children who screen positive with the benefits of an accurate diagnosis and intervention plan. This can lead to improved access to services, more appropriate foster/adoptive placements and prevention of secondary disabilities.[5] The potential for direct benefit also serves as a powerful motivator for participation as demonstrated by the 98% participation rate. Maintaining a high participation rate depends in large part on the families' experiences with the screening programme. It is imperative that false-positive screening outcomes are minimised. This is achieved with the FAS Facial Photographic Analysis Software screening tool because the FAS facial phenotype is highly sensitive and specific to FAS.[5,18] Growth deficiency and cognitive/behavioural dysfunction are not specific to FAS. Screening children positive for FAS, who do not have FAS, not only costs time and money to conduct unnecessary diagnostic evaluations, but more importantly, can come at a high emotional cost to families, especially to the birth mothers.

Although the FAS DPN approach to tracking the prevalence of FAS over time has many strengths, it is important to consider what factors may affect the validity of the results presented here. Although the observed decline in FAS was statistically significant, it is important to note that the prevalence estimates within each birth cohort are limited by the small samples sizes. Two factors, however, support the validity and stability of these interim results. First, the prevalence estimates are based on near complete (98%) ascertainment of the eligible population and thus it is highly unlikely that any FAS cases were missed. Secondly, when we look forward in time to all 908 children screened to date in this ongoing screening programme, a significant decline in the prevalence of children screening positive for FAS continues to be observed across the subset of 383 children born between 1993 and 1998 (chi-square = 4.03, $P = 0.04$). For comparison, the CDC also recognised the impact of small sample sizes on the precision of prevalence estimates, thus they required a minimum of 30 respondents and a response rate of >70% before prevalence estimates could be reported from the PRAMS data.[23] These criteria were met or exceeded in this FAS prevalence study. An obvious solution to small sample sizes is to expand the screening statewide and discussions are underway to do that.

One of the key goals of surveillance is to assess the effectiveness of primary prevention. This approach to tracking the prevalence of FAS over time in a high-risk foster care population offers an interesting alternative to tracking the prevalence of FAS across an entire state population. If statewide prevention efforts and statewide reduction in maternal alcohol use are effectively reducing the prevalence of FAS in this foster care population, it would be difficult to argue that similar reductions are not also being realised across the entire general population. The same can be said for the impact of prevention efforts on the full spectrum of disorders caused by prenatal alcohol exposure. If maternal drinking during pregnancy is reduced, the full spectrum of disorders caused by that drinking will be reduced, not just the disorder called FAS.

Although there is tremendous merit and value in tracking the prevalence of individuals damaged by prenatal alcohol exposure who do not meet the diagnostic criteria for FAS, an accurate and valid screening tool to achieve this does not currently exist. Until such time, reduction in maternal drinking during pregnancy and reduction in the prevalence of FAS in foster care can serve as valid proxy measures for reduction of the full spectrum of disorders associated with prenatal alcohol exposure across the general population.

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Fetal Alcohol Syndrome:

Guidelines for Referral and Diagnosis

National Center on Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention
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in coordination with

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Foreword

The National Center on Birth Defects and Developmental Disabilities at the Centers for Disease Control and Prevention, in collaboration with the National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effect, is pleased to present ***Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis.*** This document represents the deliberations of clinicians, researchers, parents, and representatives of governmental and non-governmental organizations, whose main goals were to increase the identification of individuals with fetal alcohol syndrome (FAS) using uniform criteria, and to improve the delivery of appropriate services to those individuals and their families. These new guidelines will help achieve those goals by educating medical and allied health professionals about FAS.

In 2003, we, in the FAS research and practice communities, celebrated the 30th anniversary of the first reports describing fetal alcohol syndrome. Since that time we have learned a great deal about this preventable condition. We now recognize that FAS represents the tip of the iceberg and that there is a continuum of outcomes associated with prenatal exposure to alcohol. These guidelines were undertaken, in part, as an effort to facilitate further identification, understanding, and study of all conditions resulting from prenatal exposure to alcohol. They build on previous work and incorporate important scientific and clinical knowledge that has been obtained in recent years. CDC is pleased to provide continuing support for the expansion and refinement of scientific descriptions for FAS and other disorders related to prenatal exposure to alcohol through its ongoing work with the National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effect and the federal Interagency Coordinating Committee on Fetal Alcohol Syndrome (ICCFAS).

Preventing all adverse outcomes associated with prenatal alcohol exposure remains a primary goal of CDC, as well as the entire U.S. Department of Health and Human Services. CDC is committed to working with other federal agencies, organizations in the private sector, relevant partners, and the public to achieve this goal. Similarly, CDC is committed to enhanced early identification of individuals with FAS and related disorders to ensure their access to appropriate services. These latest guidelines for referral and diagnosis are an important step towards that goal. Together we will ensure all persons with FAS and related disorders develop optimally and reach their full potential.

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Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis

EXECUTIVE SUMMARY

As part of the fiscal year 2002 appropriations funding legislation, the U.S. Congress mandated that the Centers for Disease Control and Prevention (CDC), acting through the National Center on Birth Defects and Developmental Disabilities (NCBDDD) Fetal Alcohol Syndrome (FAS) Prevention Team and in coordination with the National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effect (NTFFAS/FAE), other federally funded FAS programs, and appropriate non-governmental organizations, would:

- Develop guidelines for the diagnosis of FAS and other negative birth outcomes resulting from prenatal exposure to alcohol,
- Incorporate these guidelines into curricula for medical and allied health students and practitioners, and seek to have them fully recognized by professional organizations and accrediting boards, and
- Disseminate curricula to and provide training for medical and allied health students and practitioners regarding these guidelines.

Through the coordinated efforts of CDC, the NTFFAS/FAE, and a scientific working group (SWG) of experts in FAS research, diagnosis, and treatment, the following diagnostic criteria were developed over a 2-year period:

Facial dysmorphia
Based on racial norms, individual exhibits all three characteristic facial features:

- Smooth philtrum (University of Washington Lip-Philtrum Guide rank 4 or 5)
- Thin vermillion border (University of Washington Lip-Philtrum Guide rank 4 or 5)
- Small palpebral fissures (at or below 10th percentile)

Growth problems
Confirmed prenatal or postnatal height or weight, or both, at or below the 10th percentile, documented at any one point in time (adjusted for age, sex, gestational age, and race or ethnicity).

Central Nervous System Abnormalities

I. Structural

1) Head circumference (OFC) at or below the 10th percentile adjusted for age and sex.
2) Clinically significant brain abnormalities observable through imaging.

II. Neurological
Neurological problems not due to a postnatal insult or fever, or other soft neurological signs outside normal limits.

III. Functional
Performance substantially below that expected for an individual's age, schooling, or circumstances, as evidenced by:

1. Global cognitive or intellectual deficits representing multiple domains of deficit (or significant developmental delay in younger children) with performance below the 3rd percentile (2 standard deviations below the mean for standardized testing)

or

2. Functional deficits below the 16th percentile (1 standard deviation below the mean for standardized testing) in at least three of the following domains:

a) cognitive or developmental deficits or discrepancies
b) executive functioning deficits
c) motor functioning delays
d) problems with attention or hyperactivity
e) social skills
f) other, such as sensory problems, pragmatic language problems, memory deficits, etc.

Maternal Alcohol Exposure
I. Confirmed prenatal alcohol exposure
II. Unknown prenatal alcohol exposure

Criteria for FAS Diagnosis
Requires all three of the following findings:
1. Documentation of all three facial abnormalities (smooth philtrum, thin vermillion border, and small palpebral fissures);
2. Documentation of growth deficits
3. Documentation of CNS abnormality

A primary goal of these guidelines is to provide standard diagnostic criteria for FAS so that consistency in the diagnosis can be established for clinicians, scientists, and service providers. The guidelines are based on state-of-the-art scientific research, clinical expertise, and family input regarding the physical and neuropsychological features of FAS. The SWG sought to harmonize these guidelines with other diagnostic systems currently in use in this country and others (e.g., Canada). The SWG strove to provide a balance between conservative and overly inclusive diagnostic systems. Differential diagnosis from other genetic, teratological, and behavioral disorders was emphasized.

In addition to diagnostic guidelines, guidance about medical, educational, social, and family services appropriate for individuals with FAS and their families are reviewed. Services that are applicable to all individuals with FAS and their families, as well as age-specific services, are included. Such services focus on increasing parent and professional knowledge of FAS, characteristics of the disor-

der, differences between FAS and other disorders, and appropriate techniques for parenting or educating affected individuals.

Prevention of FAS and related disorders is of tremendous public health importance. A large amount of research in recent years has enabled researchers and service providers to develop programs that are effective and targeted to specific populations for reducing the risk of an alcohol-exposed pregnancy, which prevents FAS. This research is reviewed herein and recommendations for identifying and intervening with women at risk for an alcohol-exposed pregnancy are provided.

Finally, these guidelines are not intended to be an endpoint in the discussion of diagnosing FAS. There is a great need to acquire science-based information that will facilitate diagnostic criteria for additional related disorders, such as Alcohol Related Neurodevelopmental Disorder (ARND). These guidelines conclude with a call for further research and continuous refinement of the diagnostic criteria for FAS and related conditions so that affected individuals and their families can receive important services that enable them to achieve healthy lives and reach their full potential.

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Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis

Substantial empirical and clinical scientific evidence has shown that prenatal exposure to alcohol causes damage to the developing fetus. Such exposure is commonly cited as the leading preventable cause of birth defects and developmental disabilities (1-3). Children* exposed to alcohol during fetal development can suffer multiple effects. While the number and severity of negative effects can range from subtle to serious, the negative consequences are lifelong. The effects of prenatal exposure to alcohol and basic diagnostic features of fetal alcohol syndrome (FAS) were first described in the United States (U.S.) medical literature 30 years ago (4-8). In 1981, the U.S. Surgeon General issued a public health advisory warning that alcohol use during pregnancy could cause birth defects (9). Further, mandated labeling of alcohol products was established in 1989 (10). Despite the known adverse effects of prenatal exposure to alcohol, many children who experience these adverse effects do not receive proper diagnosis due to the absence of current diagnostic guidelines. These current guidelines, which were federally mandated of the Centers for Disease Control and Prevention (CDC) in the U.S. Department of Health and Human Services (DHHS) 2002 Appropriations Bill, seek to update and refine diagnostic and referral criteria in light of the scientific and clinical advances in the understanding of this disorder during the past 30 years.

These guidelines are organized into several sections. Background information and a history of the development of these guidelines are presented. Next, revised and refined diagnostic and referral criteria for FAS are described, including the empirical and clinical evidence that support each criterion. Comparison of these guidelines with other diagnostic methods currently in use is provided. Because diagnosis is not the endpoint for most clinicians who see children with FAS, a discussion of the essential services for affected individuals is included. Likewise, prevention of FAS by reducing the number of alcohol-exposed pregnancies is inherent in dealing with the disorder. Therefore, a discussion focused on identifying and intervening with women at risk for an alcohol-exposed pregnancy is provided. Finally, a discussion of future needs and efforts related to FAS and other prenatal alcohol-related disorders conclude this report.

BACKGROUND

Prevalence. Studies by CDC have reported FAS prevalence rates from 0.2 to 1.5 cases per 1,000 births across various populations (11-14). Other studies reflecting a variety of ascertainment methodologies have produced estimates ranging from 0.5 to 2.0 cases per 1,000 live births (15-16). Such rates are comparable with or above other common developmental disabilities such as Down syndrome or Spina Bifida (17). Using the CDC FAS estimates, among the approximately 4 million infants born each year, an estimated 1,000 to 6,000 will be born with FAS. Studies of particularly vulnerable populations yield prevalence estimates that far exceed those of other common disabilities. Disadvantaged groups, Native Americans, and other minorities have been documented to have

* Although referral and diagnosis for FAS can be made throughout the lifespan, the majority of individuals are referred and diagnosed in childhood. Thus, the terms “child” or “children” as used in these guidelines are not intended to preclude referral, assessment, and diagnosis of older individuals.

rates as high as three to five FAS affected children per 1,000 children (18-20). Available data also suggest that poverty is strongly associated with women's alcohol use before and during pregnancy, leading to an excess of children with FAS in impoverished groups (21-22).

The magnitude of the problem is even greater when the risk of FAS is considered by looking at the rate of alcohol-exposed pregnancies. In 1999, over half of all U.S. women of childbearing age reported alcohol consumption in the past month (23). The large majority of these women drank only occasionally, but 15% could have been classified as moderate or heavy drinkers (24-25). During that same period, 13% of women reported consuming five or more drinks on one occasion (binge drinking) in the past month (26). Given that nearly half of all U.S. pregnancies are unintended, and that millions of fertile women are sexually active while not using adequate contraception, an estimated 2% of women could be at risk for an alcohol-exposed pregnancy annually (27). More recently, higher rates have been found among subgroups of women, such as those treated for alcohol and drug problems, and women who have been incarcerated (28). Alcohol-related risk factors include drinking during pregnancy, pattern of alcohol use, alcohol dependence, use of multiple substances, having had a previous alcohol-exposed pregnancy, and having a partner or family member who drinks heavily (29-31). Women who receive little or no prenatal care, are unemployed, are socially transient, have lost children to foster or adoptive care because of neglect, abuse, or abandonment are more likely to have high alcohol use patterns that could affect a pregnancy (22,32). National survey data indicate that, while the percentage of women who abstain from alcohol use during pregnancy has increased slightly in recent years, 13% of women continue to use alcohol during pregnancy (26). Among pregnant women, approximately three percent report binge drinking (i.e., five or more drinks on any one occasion) or frequent drinking (i.e., seven or more drinks per week or five or more drinks on any one occasion) (1,33-34). Clearly, current prevalence rates of affected individuals and alcohol-exposed pregnancies indicate that the magnitude of the problem of FAS is a significant public health concern. However, because of the challenges of establishing accurate and timely prevalence information, the magnitude could be even greater than current data indicate.

Challenges in determining accurate prevalence. Despite the progress made over the past several decades to accurately establish and monitor the prevalence of FAS, the full magnitude of the problem is still not known. Primary care providers and others who care for children do not routinely or consistently identify individuals with FAS, which hinders efforts to account for these children in routine birth defects and developmental disabilities monitoring programs. Studies using multiple data sources (e.g., birth certificates, clinical charts, and medical records) show wide variations in identification of FAS cases depending on the population being surveyed (15,34). Four major factors lead to widespread failure to recognize FAS in primary pediatric care settings resulting in underestimates of the prevalence and impact of FAS (36-38):

- **No specific and uniformly accepted diagnostic criteria have been available.** The four broad areas of clinical features that constitute the diagnosis of FAS have remained essentially the same since first described in 1973: selected facial malformations, growth retardation, Central Nervous System (CNS) abnormalities, and maternal alcohol consumption during pregnancy. These four areas were reaffirmed in a 1996 report by the Institute of Medicine (IOM; 39-40). However, these broad areas of diagnostic criteria are not sufficiently specific to ensure diagnostic accuracy, consistency, and reliability . For example, clinicians do not have guidance about how many facial features must be present or the timing and severity of growth retardation needed to constitute

FAS diagnostic criteria. Thus, health providers are hampered in their efforts to screen and identify children with FAS.

- **FAS diagnosis is based on clinical examination of features, but not all children with FAS look or act the same.** Because each of the symptoms has a broad range of differential diagnoses, it is easy for a clinician to miss or misdiagnose FAS. Previous guidelines, including those included in the 1996 IOM report, did not account for children of different racial and ethnic groups or individuals of different ages . In addition, symptoms such as growth impairment, cognitive impairment, and learning disabilities can have a range of causes. Some of these causes or disorders have higher visibility and recognition than FAS, leading to misdiagnosis (or at least failure to include FAS in the total diagnosis). For instance, physicians are aware of the high prevalence of Attention Deficit, Hyperactivity Disorders (ADHD), but might not link attention problems to FAS. Without clear diagnostic criteria and instruction on their use, providers will continue to under-identify and under-diagnose FAS.

- **Lack of knowledge and misconceptions among primary care providers.** Many professionals believe that FAS can only occur if the mother is an alcoholic. Few know about the full range or progressive nature of the neurobehavioral symptoms that result from prenatal exposure to alcohol. Some incorrectly believe that FAS only occurs among low-income families or in Native American or other racial and ethnic minority groups (21). Better information on the impact of FAS among all populations and dissemination of race or ethnic variations in the diagnostic criteria can help clinicians understand the risk of prenatal alcohol exposure across populations. Knowledge about subpopulation variations in facial characteristics as well as growth curves for infants by gestational age also are important considerations (41).

- **Lack of diagnostic criteria to distinguish FAS from other alcohol-related conditions.** Creating and using diagnostic guidelines for FAS is a starting point for better defining the continuum of conditions related to prenatal alcohol exposure (40). FAS is a severe outcome of prenatal alcohol exposure. Other outcomes also occur and can result in major deficits. Terms such as Fetal Alcohol Effect (FAE), Alcohol-related Birth Defect (ARBD), and Alcohol-Related Neurodevelopmental Disorder (ARND) have been used to describe a spectrum of conditions related to prenatal alcohol exposure.

These four challenges indicate that what is urgently needed to advance the field of FAS diagnosis are current diagnostic guidelines based on empirical evidence as well as clinical experience. Such guidelines should be based on up-to-date scientific evidence and current clinical practices. Further, such guidelines would allow public health and service professionals to better determine the impact of FAS, and deliver needed services to affected children.

Congressional mandate. As part of the fiscal year 2002 appropriations funding legislation, Congress mandated that CDC, acting through the National Center on Birth Defects and Developmental Disabilities (NCBDDD) and in coordination with the National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effect (NTFFAS/FAE), other federally funded FAS programs, and appropriate nongovernmental organizations, would:

- Develop guidelines for the diagnosis of FAS and other negative birth outcomes resulting from prenatal exposure to alcohol;

- Incorporate these guidelines into curricula for medical and allied health students and practitioners, and seek to have them fully recognized by professional organizations and accrediting boards; and
- Disseminate curricula to and provide training for medical and allied health students and practitioners regarding these guidelines.

Limit in scope. The mandate to CDC indicates that, in addition to guidelines for FAS, guidelines should be developed for other negative birth outcomes resulting from prenatal exposure to alcohol. However, it was subsequently determined through discussions with all interested stakeholders that the best course was to first develop guidelines for the full FAS diagnosis (see following). Then, in subsequent efforts, these guidelines could be expanded or refined to include other alcohol-related disorders. This approach was determined to provide the most timely and scientifically grounded guidelines at this time. However, this decision does not curtail ongoing efforts to define conditions beyond FAS or develop diagnostic guidelines for those conditions.

Note on terminology. Many terms are used to describe the continuum of effects that result from prenatal exposure to alcohol, including: Fetal Alcohol Effect, Alcohol-related Birth Defects, and Alcohol-Related Neurodevelopmental Disorder. A more recent term that has been introduced is Fetal Alcohol Spectrum Disorders (FASD). In April 2004, several federal agencies [(National Institutes of Health (NIH), CDC, & Substance Abuse and Mental Health Services Administration (SAMHSA)] along with experts in the field were convened at a summit sponsored by the National Organization on FAS (NOFAS) to develop a consensus definition of FASD. The resulting definition, adopted in these guidelines, is:

> *Fetal Alcohol Spectrum Disorders (FASD) is an umbrella term describing the range of effects that can occur in an individual whose mother drank alcohol during pregnancy. These effects may include physical, mental, behavioral, and/or learning disabilities with possible lifelong implications. The term FASD is not intended for use as a clinical diagnosis.*

APPROACH AND METHODS FOR DEVELOPMENT OF GUIDELINES

To meet its Congressional mandate, CDC convened an internal working group, led by staff from the FAS Prevention Team of NCBDDD, to conduct preplanning meetings to determine the best methods for development of all aspects of the guidelines: (a) general framework for referral and diagnosis, (b) development of guidelines for physical features (dysmorphia and growth) as well as exposure, and (c) development of guidance to clinicians concerning potential CNS abnormalities. Each of these aspects involved review of the literature, as well as discussions with consultants, clinicians, researchers, and parents of affected children. A description of general and specific methods of development of each aspect follows.

General review of literature. CDC staff identified various reports and documents to be used as the scientific basis for diagnostic guidelines. The science base for this work included, but was not limited to:

- Published scientific, peer-reviewed, literature on physical and neurodevelopmental effects of prenatal exposure to alcohol;
- The report of the IOM Committee to study FAS (40);
- Results from the work of the NTFFAS/FAE (42) ;
- Criteria from standard, widely used dysmorphology and neurodevelopmental textbooks or guides (40,43-44);
- Research on measuring the FAS facial phenotype (45-47);
- Reports on systems that operationally interpret the 1996 IOM criteria(48-50);
- Experience in developing a surveillance case definition for the Fetal Alcohol Syndrome Surveillance Network (FASSNET) (51);
- Ongoing state surveillance and research data, particularly work of Alaska (19,35,52), Colorado (53), New Jersey, Nevada, Washington, and the Four State FAS Consortium (consisting of North Dakota, Montana, Minnesota, and South Dakota);
- The American Academy of Pediatrics (AAP) August 2000 statements and recommendations on FAS and other effects related to maternal alcohol use (54); Position of the American Academy of Family Physicians, which refers to the AAP statement; and
- Canadian National Committee's efforts concerning standardization of guidelines for screening, diagnosis, and surveillance of FAS.

Framework. Before developing the specifics of the diagnostic and referral guidelines, CDC staff determined that it would be helpful to conceptualize the entire diagnostic and referral process encountered by affected individuals and their families. Such a framework also would assist professionals in understanding their specific role in the referral and diagnostic process, as well as guide them with next steps for each case. The framework was reviewed by health care policy consultants as well as members of the NTFFAS/FAE. Revisions were made based on their suggestions. This framework is presented in detail later in these guidelines.

Creation of the Scientific Working Group. The first step in development of the guidelines was to convene an internal CDC working group. The group consisted of members of the NCBDDD FAS prevention team, geneticists, developmental pediatricians, epidemiologists, and psychologists, as well as other allied health professionals. This internal working group developed a list of potential external experts who could be convened to develop the actual guidelines. The large external panel of experts was designated as a scientific advisory panel. From this panel, a subset of experts formed a Scientific Working Group (SWG) that delineated the specifics of the diagnostic criteria.

The external SWG convened by CDC included researchers, clinicians in general and specialty medicine, representatives from academic centers and state health agencies, as well as consumer representatives from the National Organization on FAS (NOFAS) and The Arc of the United States. The scientific advisory panel met in Atlanta, Georgia, on July 12, 2002, to begin deliberations on the proposed guidelines. At that meeting, four subgroups were created: FAS Referral and Diagnosis; ARND issues; Essential Services for Children with FAS/ARND; and Identifying and Intervening with Women at Risk for an Alcohol-Exposed Pregnancy. The subgroups met and began deliberations related to the guidelines in their respective topic areas.

A subsequent meeting of the SWG occurred on September 20, 2002, in conjunction with an NTFFAS/FAE meeting, also in Atlanta. This offered the opportunity for information sharing and feedback on progress made thus far from a range of stakeholders represented on the NTFFAS/FAE

(e.g., parents, providers, and researchers). The FAS Referral and Diagnostic subgroup and the Essential Services subgroup met to further deliberate on their recommendations. The recommendations from these two subgroups were then presented to the NTFFAS/FAE for review and input. The component of the criteria for FAS screening and diagnosis that presented the most difficulty to the FAS Referral and Diagnosis subgroup was the central nervous system (CNS)/neurobehavioral component. This group felt that members of the ARND subgroup were most qualified to develop that particular component of the criteria.

The ARND subgroup drew important information from a poll of the experts that was conducted to identify the CNS/neurobehavioral domains most affected by prenatal alcohol exposure (further description follows). Results of this poll were incorporated into the FAS Referral and Diagnosis Guidelines within the CNS/neurobehavioral component. The third meeting of the FAS Referral and Diagnosis subgroup was teleconferenced on March 11, 2003, and draft guidelines were reviewed and revised. At that time and based on review of the available scientific evidence concerning diagnosis of ARND, the scope of the guidelines was limited to FAS, with future efforts to be devoted to other prenatal alcohol-related disorders. This revised version of the diagnostic criteria was presented to and approved by the NTFFAS/FAE on March 13, 2003 with recommendations. Consensus among members of the external SWG and the NTFFAS/FAE was used to finalize each criterion of the guidelines for dysmorphology, growth, and prenatal exposure to alcohol. At the December 8 and 9, 2003, meeting of the NTFFAS/FAE, further discussions were held regarding the CNS/neurobehavioral criteria and subsequent revisions were made. Finalization of the FAS criteria was reached during a teleconference of the NTFFAS/FAE on May 13, 2004.

Highlights of deliberations of SWG: Physical criteria. The SWG concluded that a strict definition of FAS should be established first, not including diagnostic terms such as fetal alcohol effect (FAE), alcohol-related neurodevelopment disorder (ARND), and alcohol-related birth defect (ARBD) at this time because of insufficient scientific evidence on which to base diagnostic criteria for these related conditions. The SWG urged that CDC diagnostic guidelines for FAS use objective, quantitative measures to improve accuracy and reproducibility and apply specific case definitions guided by evidence-based knowledge and new technologies. The SWG also recommended use of racial and ethnic norms for facial features, head circumference (occipitofrontal circumference, OFC), and other key features when available.

During its deliberations, the SWG acknowledged the need to keep recommendations for the diagnosis of FAS relevant to practitioners working in clinical settings. Also, the SWG acknowledged differences between screening, diagnosis, surveillance, and research activities and the separate definitional needs of each of these activities. Effective tools and practical strategies for primary care settings were considered. The SWG encouraged CDC to call for action and collaboration among obstetricians, pediatricians, family practice physicians, and others providing primary care and screening services to children. The SWG also discussed the need for more data regarding the range of essential services for children who are diagnosed positive for FAS and stressed the importance of a multidisciplinary plan for care that links to the child's community healthcare provider or medical home.

Central nervous system abnormality criteria. Because the scientific evidence and professional consensus on CNS criteria are not yet at the level of specificity equal to that available for physical features, a different approach was used in developing CNS criteria. Further, it was decided that rather than

creating strict criteria for specific CNS domains and level of severity needed, more general guidelines should be described. Such general guidelines should assist the clinician in identifying areas of deficit most likely to be found with individuals who have FAS, as well as individuals with FAS who have less common types of deficits. This approach was considered optimal because a number of structures of the brain are affected versus a single, isolated structure. This generalized nature of damage from prenatal alcohol exposure can result in a wide array of neurodevelopmental outcomes.

To develop such neurodevelopmental guidelines for referral and diagnosis for FAS, the ARND/CNS subgroup polled clinicians and researchers who have extensive knowledge and experience with individuals who have FAS or other related diagnoses. These experts were individuals who specialize in neurobehavioral issues, have extensive research and clinical experience making the FAS/ARND diagnosis, and have contact with families and children with FAS. They were queried to find out what behavioral domains they encountered most frequently or were most essential for making an FAS/ARND diagnosis. Twenty-two clinicians were contacted and their responses were synthesized. The clinicians were asked to identify five areas of deficit they considered most important for diagnosis of FAS or related disorders. In addition, the clinicians were also asked to identify three to five specific behaviors that could be used as examples of each of the five areas of deficit.

The resulting guideline of neurodevelopmental features associated with FAS are presented as being as inclusive as possible, while understanding that certain areas of neurodevelopmental functions are more vulnerable to prenatal exposure to alcohol. Each domain is presented so as to include exemplars from direct observation or parent report that can be documented through standardized testing.

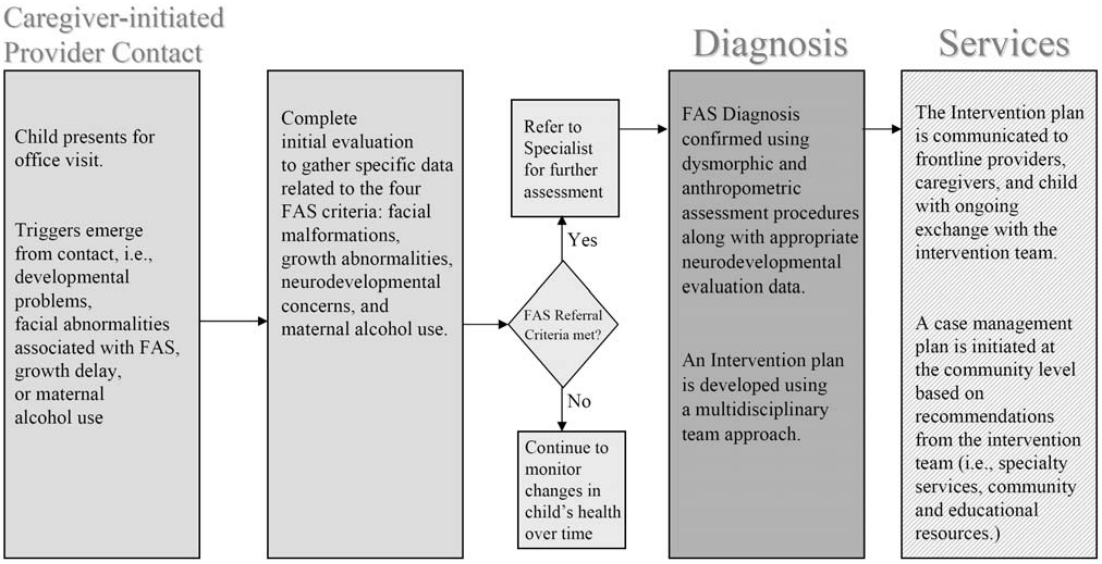
Medical diagnostic criteria are generally evaluated in two ways: (1) the criteria must be reliable and; (2) the criteria must be as valid as possible. The criteria that appear in these diagnostic guidelines meet both of these requirements. In developing these diagnostic guidelines, the SWG also considered the feasibility of applying the criteria in primary care practice and related settings where children are seen.

DIAGNOSTIC AND REFERRAL FRAMEWORK

The framework in Figure I was developed to help guide the discussions of the SWG as they deliberated on the guidelines for referral and diagnosis of FAS. The framework was developed to provide an overview of the entire identification, referral, diagnosis, and treatment process. This overview guided the SWG in identifying key points that needed to be addressed to develop specific guidelines. The framework reflects CDC's recommendation that developmental screening be implemented to improve children's health and help them reach their full potential. A discussion of the major points of the framework follows.

Initial identification. Initial recognition that a child or older individual has a potential problem can come from many sources. Often, parents notice differences between a child and his or her siblings. School systems, including Head Start and daycare staff, interact with a large number of children and often recognize when someone is having difficulty. Social service professionals, such as WIC clinic staff, social workers, and foster care agencies frequently recognize children and individuals having difficulty and needing evaluation. And finally, healthcare providers (particularly pediatricians) often are the first to screen for and detect problems; or obstetricians, who might be aware of

FIGURE 1. Framework for FAS Diagnosis and Services



a maternal substance abuse problem, might refer a newborn. Recognition of many of the problems associated with FAS is exactly the type of condition the "well child" visits to the doctor's office are meant to identify. It is assumed that triggers, such as facial abnormalities, growth delay, developmental problems, or maternal alcohol use, will emerge from the contact. Recognition of a potential problem should lead the provider, regardless of specific profession, to facilitate getting the person and his or her family to the appropriate next step.

Referral. The referral process is initiated at the point a clinician starts to have suspicions of an alcohol-related disorder for a child. This process is facilitated by thorough knowledge of the physical and neurodevelopmental domains affected in individuals with FAS, as well as characteristics that could trigger a referral. Examples of triggers are presented later, in the Referral section of these guidelines. In making a referral for a complete diagnostic evaluation for FAS, it is helpful for the referring provider to gather and document specific data related to the FAS criteria. These data will assist the provider in making the decision to diagnose the child or to refer the child to a multidisciplinary evaluation team for a confirmed diagnosis. In addition, these data could be forwarded to the multidisciplinary evaluation team to guide the diagnostic process. A complete review of systems, noting features consistent with FAS, would be most productive.

Diagnosis. At this stage, the child would be presented to a multidisciplinary team who would engage in a more thorough assessment of the child using FAS diagnostic procedures to evaluate dysmorphia and growth parameters, as well as obtain appropriate neurodevelopmental evaluation data. Once a diagnosis is made, an intervention plan would be developed using a multidisciplinary team approach. A variety of specialists could contribute to the multidisciplinary team, including dysmorphologists, developmental pediatricians, psychiatrists, psychologists, social workers, and educational specialists. Other clinicians, such as pediatricians and family practitioners, also might make the FAS diagnosis, with appropriate training in use of these guidelines. In many rural and less populated regions, these clinicians must make the diagnosis for many types of birth defects and developmental

disabilities. Many of these evaluation services are available within the community setting, for example school systems could provide neurocognitive assessments.

DIAGNOSTIC CRITERIA

Dysmorphia. Human congenital malformations are referred to as dysmorphic features or dysmorphia (55). Dysmorphia occurs when normal morphogenesis is interrupted, creating a particular feature which is shaped, sized, or positioned outside the normal range of development. Alcohol is a teratogen that results in dysmorphia through interference with nerve cell development and functioning, alterations in the ability of cells to grow and survive, increased formation of cell-damaging free radicals, altered pathways of biochemical signals within cells, and altered expression of certain genes and genetic information. In short, alcohol has been shown to interfere with fetal nerve cell development and function in a variety of ways (56-57).

In first describing the dysmorphic features of FAS, Jones and colleagues focused on short palpebral fissure, maxillary hypoplasia (with prognathism), and the presence of epicanthal folds that were observed for a majority of the children described. However, other features also were noted for some patients, including altered palmar fexional crease patterns (i.e., hockeystick crease), cardiac anomalies, joint disability, overlapping fingers, ear anomalies, hemangiomas, ptosis, hypoplastic nails, and pectus deformities (4,5). Over the next 30 years, additional features described included: microcephaly, short nose, smooth philtrum with thin vermillion border, cleft lip, micrognathia, protruding auricles, short or webbed neck, vertebra and rib anomalies, short metacarpal bones, menigomyelocele, hydrocephalus, and hypoplastic labia majora (43).

Despite the heterogeneity of expression for dysmorphic features related to prenatal exposure to alcohol, core facial dysmorphia have emerged through human and animal studies. Experimental studies with a mouse model and primates indicate that the facial dysmorphia observed for individuals with FAS are the result of disturbances of cellular migration during organogenesis along the midline of the face (58). Using anthropomorphic measurements of all facial features, clinical researchers have confirmed the midline feature abnormalities (59). Studies of clinic-referred samples also support these features as discriminant for FAS (60-61). Based on these scientific findings and the extensive clinical experience of the SWG, the following facial dysmorphic features were determined to meet the dysmorphia criteria essential for FAS (based on racial norms):

- Smooth philtrum (measured as 4 or 5 on Lip-Philtrum Guide*)
- Thin vermillion border (measured as 4 or 5 on Lip-Philtrum Guide) (i.e., upper lip)
- Small palpebral fissures (measured as ≤10th percentile according to age and racial norms)

The individual must exhibit all three characteristic facial features; however, additional features also can be present. For example, maxillary hypoplasia is often noted for individuals with FAS as well as those associated features described previously. Cross-sectional and longitudinal studies indicate that many features can change with age or development. After puberty, the characteristic facial features associated with FAS can become more difficult to detect (62). However, recent findings indicate that these three key features remain for the majority of individuals with FAS (47,50).

* University of Washington Lip-Philtrum Guide (49-50).

Use of these three cardinal features (smooth philtrum, thin vermillion border, and small palpebral fissures) to assess whether an individual's dysmorphia is consistent with FAS, is compatible with the IOM report and other diagnostic systems currently in use. Specific criteria were chosen by the SWG to maximize inclusiveness of potential cases on this diagnostic parameter and, therefore, might differ somewhat from other systems currently in use. For example, the 1999 version of University of Washington 4-digit code system uses the same philtrum and vermillion border criteria (as noted by reference to its Lip-Philtrum Guide), but uses a cutoff of the 3rd percentile (2 or more standard deviations below the norm) for palpebral fissures , which is a more conservative cutoff (50). This more conservative approach results in fewer individuals meeting the dysmorphia criteria for an FAS diagnosis but also reduces potential false positives for the diagnosis. Other ways to assess dysmorphia for the FAS diagnosis include checklists or weighted checklists (63-65). Of those checklists reviewed by the SWG, all designated the philtrum, vermillion border, and palpebral fissures as the cardinal facial features of FAS (either by higher weighting or explicit notation). However, because of the cumulative nature of some such lists, an individual who has several of the associated features but not the cardinal features could still be given the FAS diagnosis. Thus, the checklists tend to be more inclusive than the current guidelines, with greater potential for false-positive diagnoses. Review of available diagnostic systems seems to indicate that the dysmorphic criteria agreed upon by the SWG provide a balance between conservative and overly inclusive diagnostic systems.

Differential diagnosis of dysmorphia. Individual dysmorphic features are not unique to any particular syndrome. Even rare defects or certain clusters of dysmorphic features can appear in a variety of syndromes. Therefore, a process of differential diagnosis is essential in making an accurate FAS diagnosis. Following, in Table 1 is a list of syndromes with dysmorphic features that overlap with the primary features of the FAS diagnosis (43). As can be seen from Table 1, none of the syndromes with single overlapping features (except for Toluene embryopathy) have the full constellation of small palpebral fissures, thin vermillion border, and smooth philtrum. However, there are some syndromes in which the constellation of features (primary, occasional features, or both) give a "gestalt" that is similar to the "gestalt" of FAS. These syndromes should be considered in particular when completing the differential diagnosis. Table 2 lists these syndromes, along with the overlapping and differentiating features.

Growth problems. Growth retardation, variably defined, has been documented consistently in individuals with FAS. However, these observations used a variety of parameters (e.g., height, weight, and head circumference), severity levels (below 25th percentile, below 10th percentile, or below 3rd or 2nd percentile), and timing of growth problems (current, birth or present at any point during life). The SWG reviewed available literature, clinical expertise, and practical issues to arrive at benchmarks for each of these three aspects of growth abnormalities.

The primary parameters of growth that need to be impaired to meet the growth retardation criteria of FAS are height, weight, head circumference, or a combination thereof. Anecdotally, a small number of children with FAS have been found to have disproportionate height in relation to weight. However, because multiple organic factors can lead to growth deficiencies (e.g.,. brain structure abnormalities leading to poor skeletal growth or disruption of endocrine function leading to poor weight gain), and because most children with FAS are symmetrical for height and weight (66), it was determined that deficiencies in *either* height or weight, but not height for weight, should be included as growth parameters that might be affected by FAS. Thus, children with growth retarda-

Table 1. Differential diagnosis of individual features associated with FAS

Feature	Syndromes
Smooth philtrum	Cornelia de Lange syndrome Floating-Harbor syndrome Geleophysic dysplasia Opitz syndrome Toluene embryopathy
Thin Vermillion border	Miller-Dieker (Lissencephaly) syndrome Fetal Valproate syndrome Geleophysic dysplasia Cornelia de Lange syndrome Toluene embryopathy
Small palpebral fissures	Campomelic dysplasia DiGeorge sequence Dubowitz syndrome Duplication 10q sequence Duplication 15q sequence FG syndrome Maternal phenylketonuria (PKU) fetal effects Oculodentodigital syndrome Opitz syndrome Trisomy 18 syndrome Williams syndrome Velocardiofacial syndrome Toluene embryopathy

Note: Features that discriminate these disorders from FAS can be found in Jones, 1997.

tion in height or weight would meet the growth retardation criteria for the FAS diagnosis. Consistent with poor brain development, it was determined that head circumference should be included as a CNS parameter rather than a growth parameter (67-68).

Severity of growth retardation has been defined for each parameter as at or below the 10th percentile or at or below the 3rd percentile by a majority of FAS studies. The primary issue for severity is inclusion or exclusion of children for the FAS diagnosis. Use of the 10th percentile would result in more false-positive FAS diagnoses; while use of the 3rd percentile would result in a greater number of false-negatives. For public health reasons of capturing the largest number of children who might need services, the 10th percentile was chosen by the SWG. As noted previously in the dysmorphia section, use of the 10th percentile strikes a balance among criteria used in other diagnostic systems. Again, the 1999 edition of the University of Washington 4-digit code takes a conservative approach, using the 3rd percentile as the cutoff. Checklist systems often do not specify a particular level of growth retardation and some do not specify which growth parameters should be considered (i.e., height, weight, or height relative to weight). This lack of specificity could lead to inconsistency in diagnostic method, which in turn, could lead to inconsistent application of the FAS diagnosis.

Table 2. Differential diagnosis of syndromes similar to FAS

Syndrome	Overlapping Features	Differentiating Features
Aarskog syndrome	Small nose with anteverted nares, broad philtrum, maxillary hypoplasia, and wide-spaced eyes	Rounded face, down-slant to palpebral fissures, widow's peak, crease below lower lip, incomplete out folding of upper helices, and dental eruption problems.
Williams syndrome	Short palpebral fissures, anteverted nares, long philtrum, depressed nasal bridge, and epicanthal folds	Wide mouth with full lips, stellate pattern of the iris, periorbital fullness, and connective tissue disorders.
Noonan's syndrome	Low nasal bridge, wide-spaced eyes, and epicanthal folds	Down-slant to palpebral fissures, keratoconus, wide mouth, and protruding upper lip
Dubowitz syndrome	Short palpebral fissures, wide spaced eyes, and epicanthal folds	Shallow supraorbital ridge with nasal bridge near the level of the forehead, and broad nasal tip
Brachmann-DeLange syndrome	Long philtrum, thin vermillion border, anteverted nares, and depressed nasal bridge	Single, bushy eyebrow extending across forehead, long eyelashes, downturned mouth, high arched palate, and short limbs (yielding short stature)
Toluene embryopathy	Short palpebral fissures, midface hypoplasia, smooth philtrum, and thin vermillion border	Micrognathia, large anterior fontanel, down-turned mouth corners, hair patterning abnormalities, bifrontal narrowing, and ear abnormalities
Fetal hydantoin syndrome (Fetal dilantin syndrome)	Wide-spaced eyes and depressed nasal bridge	Short nose with bowed upper lip
Fetal valproate syndrome	Epicanthal folds, anteverted nares, long philtrum with thin vermilion border, and wide-spaced eyes	High forehead, infraorbital crease or groove, and small mouth
Maternal PKU fetal effects	Epicanthal folds, short palpebral fissures, long underdeveloped philtrum, and thin vermillion border	Small upturned nose, round facies, and prominent glabella

The current guidelines provide consistent growth parameters that should be assessed, as well as a more inclusive level of the 10th percentile.

The primary issue that emerged in the discussion of timing of growth retardation was whether growth retardation needs to be present at the time of the diagnosis, or whether it could have occurred previously and been resolved. This is particularly important when including prenatal growth retardation or early growth problems due to failure to thrive. Because a great number of treatments exist for growth problems (e.g. feeding tubes or hormone therapy), the SWG adopted the criteria that any history of growth retardation, including prenatal growth deficiencies, should be allowed within the diagnostic criteria (61).

Thus, the growth retardation criteria adopted by the SWG are: confirmed prenatal or postnatal height, weight, or both at or below the 10th percentile documented at any one point in time (adjusted for age, sex, gestational age, and race or ethnicity). The committee noted that the examiner should make sure that the single point in time when the growth deficit was present does not correlate with a point in time when the child was nutritionally deprived.

Differential diagnosis of growth problems. Growth retardation and growth deficiencies occur in children, adolescents, and adults for a great many reasons. Some of the most obvious reasons have to do with insufficient nutrition. This could be a particular problem for infants with poor sucking responses who experience failure to thrive. In addition, several genetic disorders result in specific growth deficiencies (e.g., dwarfism). Prenatal growth retardation can be due to a variety of factors, including maternal smoking or other behaviors leading to hypoxia, poor maternal nutrition, or genetic disorders. Both environmental and genetic bases for growth retardation should be considered for differential diagnosis when considering the FAS diagnosis.

Central nervous system abnormalities (CNS). More than 2,000 scientific papers regarding the teratogenic effects of alcohol exposure for CNS have been published over the past 30 years (69-71). Studies of the impact of fetal exposure to alcohol show a range of short- and long-term cognitive and behavioral outcomes resulting from these CNS abnormalities. Complicating detection of these abnormalities is that FAS neurobehavioral presentation changes across the lifespan (4,61,72-79). Despite this developmental process, CNS deficits generally persist throughout the lifespan (80). Longitudinal studies have found that many adults affected by FAS have complex mental health disorders, are affected by the consequences of neurobehavioral deficits, and are unable to sustain independent living (81).Prenatal exposure to alcohol can result in an array of structural, functional, neurological problems, or a combination of these, as well as abnormalities of the CNS (40). To meet the FAS diagnostic criteria for CNS abnormality, structural, neurological, or functional deficits, or a combination thereof, must be documented. Note that it is also possible for an individual to present with more than one CNS structural, neurological, functional deficit or abnormality. Guidelines for each type of CNS abnormality follow.

I. Structural

1. Documented small or diminished overall head circumference (OFC at or below the10th percentile) adjusted for age and gender (including head circumference at birth; 4,68). For children who have overall growth deficiency (i.e., height and weight below the 10th percentile) to meet this criteria for CNS abnormality, the child's head circumference should be disproportionately small to his or her overall size (i.e., OFC at or below the 3rd percentile).

2. Clinically significant brain abnormalities observable through imaging techniques (e.g. reduction in size, or change in shape of the corpus callosum, cerebellum, or basal ganglia) as assessed by an appropriately trained professional (4,58,82-88).

   Note: An individual could meet the CNS abnormality criteria for the FAS diagnosis through a structural abnormality, yet not demonstrate detectable functional deficits.

II. Neurological

Documented evidence of neurological damage to the CNS. Neurological problems of CNS can include seizures not due to a postnatal insult or fever or other soft neurological signs outside normal limits (e.g., in coordination, visual motor difficulties, nystagmus, or difficulty with motor control; 89-92). As with head circumference, abnormal neurological findings can be most predictive of underlying CNS abnormality due to prenatal alcohol exposure, rather than later environmental factors, in younger children. The use of norm-referenced measures of neurological functioning is recommended.

III. Functional

Assessment findings that indicate deficits, problems, or abnormalities in functional skills of the CNS. Early brain damage is usually generalized rather than specific, with increased specificity of abnormalities revealed as development progresses. The functional abilities affected by prenatal exposure to alcohol vary greatly from person to person, depending on the amount of alcohol exposure, timing of exposure, and pattern of exposure (e.g., chronic exposure versus binge episodes). Despite this inherent variation in effects, several areas of significant functional vulnerability have been observed consistently by clinicians and clinical researchers with particular damage to corresponding structures reported (e.g., corpus callosum, cerebellum, or basal ganglia). Variability in exposure impact results in variability of structural, neurological, or functional deficits, or a combination thereof in affected individuals.

For functional deficits, it is generally accepted that multiple locations in the brain (and corresponding functional capability) are affected by prenatal exposure to alcohol. To address this issue, functional deficits that fulfill the CNS abnormality criteria can be met in two ways:

(1) Global cognitive deficit (e.g., decreased IQ)
or significant developmental delay in children too young for an IQ assessment;

OR

(2) Deficits in THREE or more specific functional domains

These two ways of meeting the criteria for a functional CNS abnormality were adopted because of the composite nature of cognitive/intellectual and developmental measures (93-94). Decreased performance on a standardized measure of cognition/intelligence or development assumes deficits in multiple domains. In the absence of such a measure, several specific domains need to be assessed individually to determine that multiple functional domains have been affected. The specific domains most often cited as areas of deficit or concern for individuals with FAS are described below, although other domains and abilities can be affected and this list is not exhaustive. It should

be noted that for each of the following specific domains described, other agents and environmental factors can produce deficits or outcomes similar to prenatal alcohol exposure, making care differential diagnosis essential. Finally, these descriptions are intended to be suggestive and examples of likely and possible problems a clinician might encounter then need to assess using psychometric instruments. The exemplars are not intended to be exhaustive, or to present a necessary list of behaviors to be used as a checklist without reliable and valid assessment.

a) **Cognitive deficits or significant developmental discrepancies.** It is important to note that global deficits or delays can leave the child scoring in the normal range of development, but below what would be expected for his or her environment and background (61,95-99). In addition to formal testing (either through records or current testing), behaviors that may be observed (or reported) in the clinical setting that suggest cognitive deficits or developmental delays that should be assessed by standardized testing include but are not limited to **specific learning disabilities (especially math and/or visual-spatial deficits); uneven profile of cognitive skills; poor academic achievement; discrepancy between verbal and nonverbal skills; and slowed movements or reaction to people and stimuli (e.g., poor information processing)**. (75,100-103)

b) **Executive functioning deficits.** Executive functioning (EF) is defined as the ability to maintain an appropriate problem solving set for attainment of a future goal and that this ability includes the more specific skills of inhibition, planning, and mental representation (104). Behaviors that can be observed (or reported) in the clinical setting that might indicate an EF deficit that should be assessed by standardized testing include, but are not limited to **poor organization, planning, or strategy use; concrete thinking; lack of inhibition; difficulty grasping cause and effect; inability to delay gratification; difficulty following multistep directions; difficulty changing strategies or thinking of things in a different way (i.e., perseveration); poor judgment; and inability to apply knowledge to new situations.** (105-108)

c) **Motor functioning delays or deficits.** Both gross motor and fine motor skills can be impaired for individuals with FAS (109-111). Visual-motor/visual-spatial coordination is a particularly vulnerable area of functioning (99,112-113). Behaviors that can be seen (or reported) in the clinical setting that indicate motor problems that should be assessed by standardized testing include, but are not limited to **delayed motor milestones; difficulty with writing or drawing; clumsiness; balance problems; tremors; and poor dexterity. For infants, a poor suck is often observed.** (61,114-116)

d) **Attention and hyperactivity problems.** Attention problems are often noted for children with FAS, with many children receiving a diagnosis of attention-deficit hyperactivity disorder (AD HD; 117). Although such a diagnosis can be applied, some research has shown that the attention problems for children with FAS do not seem to fit the classic pattern of ADHD. Individuals with FAS tend to have difficulty with the encoding of information and flexibility (shifting) aspects of attention; whereas children with ADHD typically display problems with focus and sustaining attention (118-119). Individuals with FAS also can appear to display hyperactivity because their impulsivity may lead to increased activity levels. Behaviors that may be observed (or reported) in the clinical setting that suggest attention problems related to FAS that should be assessed by standardized testing include, but are not limited to **described by adult as "busy"; inattentive; easily distracted; difficulty calming down; overly active; difficulty completing tasks; and/or trouble with transitions. Parents might report inconsistency in attention from day to day (e.g., "on"**

days and "off" days). (79,120-125)

e) **Social skills problems.** The executive, attention, and developmental problems described previously often lead to clinically significant difficulty for people with FAS when interacting with peers and others. Because of the mental representation problems, individuals with FAS often have social perception or social communication problems that make it difficult for them to grasp the subtler aspects of human interactions (107,126-127). Consistent difficulty understanding the consequence of behavior or inappropriate behavior is frequently described for individuals with FAS (62,80). Behaviors that can be observed (or reported) in the clinical setting that indicate these types of social difficulties that should be assessed by standardized testing include, but are not limited to **lack of stranger fear; often scape-goated; naiveté and gullibility; easily taken advantage of; inappropriate choice of friends; preferring younger friends; immaturity; superficial interactions; adaptive skills significantly below cognitive potential; inappropriate sexual behaviors; difficulty understanding the perspective of others; poor social cognition; and clinically significant inappropriate initiations or interactions.** (128-130) It should be noted that standardized assessment of social problems can be quite difficult. Social functioning is a multifaceted domain that can require several areas of assessment.

f) **Other potential domains that can be affected.** In addition to these five most often cited problem areas, deficits and problems to be assessed by standardized testing can present in several other areas, including **sensory problems (e.g., tactile defensiveness and oral sensitivity); pragmatic language problems (e.g., difficulty reading facial expression; poor ability to understand the perspectives of others); memory deficits (e.g., forgetting well-learned material, and needing many trials to remember); and difficulty responding appropriately to common parenting practices (e.g., not understanding cause-and-effect discipline)**. While abnormalities in these "other" areas have been reported for some individuals with FAS, expert consensus suggests deficits in these areas present at a lower frequency than do those in the other five specific domains (62).

> These guidelines strongly recommend that functional domains be assessed using norm-referenced standardized measures. Domains should be assessed by appropriate professionals using reliable and validated instruments.

Level of functional deficit. In these guidelines, global cognitive deficits and developmental delay, or deficits in three or more specific domains, are defined as performance substantially below that expected for an individual's age, schooling, or circumstances. Several statistical thresholds have been suggested to operationally define performance substantially below expected levels. Previous research indicates that approximately only one-quarter of individuals diagnosed with FAS perform at the most conservative level of below the 3rd percentile (2 standard deviations below the mean) on standardized measures (95). In keeping with this finding, and to adequately capture the full spectrum of effects, the SWG adopted two levels of functional deficits that would meet the criteria for a CNS abnormality: (1) for significant global cognitive deficit performance below the 3rd percentile (i.e., 2 standard deviations below the mean); and (2) for three or more specific domains performance below the 16th percentile (i.e., 1 standard deviation below the mean) on standardized measu res of individual domains. Thus, individuals scoring below the normal range on a global measure of IQ or development and individuals scoring in the below average range on standardized measures of three

specific functional domains would meet the criteria for functional CNS abnormality for diagnostic purposes.

Ideally, functional deficits should be established through appropriate standardized neuropsychological testing by a trained professional. The SWG recognized that such standardized testing might not be readily available in all diagnostic settings. Clinicians are strongly encouraged to supplement their observations by obtaining standardized testing through early intervention programs, public schools, and psychologists in private practice. The SWG emphasizes the need for psychometric testing when evaluating an individual for the FAS diagnosis, and use of clinical judgment alone could veer away from the goal of implementing standard diagnostic criteria for FAS. In addition, such testing will facilitate the development of individualized and appropriate treatment plans for diagnosed individuals. These guidelines are intended to provide information concerning the types of CNS abnormalities that might be observed, as well as the level of deficit that can be expected. In addition, they seek to support the need for quality assessments administered by trained professionals when establishing CNS abnormalities associated with the FAS diagnosis.

These guidelines for assessment of CNS abnormalities for making the FAS diagnosis is in harmony with, although not duplicative of, other diagnostic guidelines and systems. The 1999 version of the University of Washington 4-digit code and the guidelines developed by Health Canada requires performance below the 3rd percentile (2 standard deviations below the mean on standardized testing) in three separate domains in which global deficits count as one domain. Some health systems might find this approach useful in situations in which resources for standardized testing are readily available.

Mental health problems and lifelong consequence. Difficulty in any of the functional CNS areas described above can lead to maladaptive behavior and mental health problems with lifelong consequences. Commonly co-occurring mental health issues (excluding attention problems) reported by clinicians and cited in the scientific literature to date, include ***conduct disorders, oppositional defiant disorders, anxiety disorders, adjustment disorders, sleep disorders, and depression*** *(81,95,131-134)*. Although attention problems can be classified as a mental health issue or psychiatric condition, in these guidelines they are treated as a primary deficit resulting from alcohol-related CNS damage, rather than a secondary mental health issue. There are considerable animal, human, and clinical studies that document attention deficits for many individuals with prenatal exposure to alcohol (117). In addition, decreased adaptive skills and increased problems with daily living abilities have been consistently documented, although further research is needed . Such problems include dependent living conditions, disrupted school experiences, poor employment records and encounters with law enforcement (including incarceration; 95). Although these mental health and very debilitating lifelong consequences should not be used for the purpose of diagnosis, it should be noted that they are very prevalent among individuals with FAS and are very likely to be the presenting conditions that should trigger a referral and comprehensive diagnostic evaluation.

Differential diagnosis of CNS abnormalities. Differential diagnosis of CNS abnormities involves not only ruling out other disorders but also specifying co-occurring disorders. The CNS deficits associated with FAS, in particular functional deficits, can be produced by many different factors in addition to prenatal alcohol exposure. It is important to determine that the observed functional deficits are not better explained by other causes. In addition to other organic syndromes that produce deficits in one or more of the previously cited domains (e.g., Williams syndrome and Down syn-

drome), significantly disrupted home environments or other external factors can produce functional deficits in multiple domains that overlap with the domains that are affected by FAS. In making the differential diagnosis of FAS by ruling out other syndromes, CNS abnormalities should be evaluated in conjunction with dysmorphia and laboratory findings. The more difficult differentiation is for CNS abnormalities resulting from environmental influences (e.g., abuse or neglect, disruptive homes, and lack of opportunities). ***To assist with differential diagnosis between FAS and environmental causes for CNS abnormalities it is important to obtain a complete and detailed history for the individual and his or her family.***

In addition to ruling out other causes for CNS abnormalities, a complete diagnosis should identify and specify other disorders that can co-exist with FAS (e.g., autism, conduct disorder, and oppositional defiant disorder). ***It is very important to note that a particular individual might have a conduct disorder in addition to FAS, but that not all persons with a conduct disorder have FAS and not all individuals with FAS will have a conduct disorder.*** Thus, organic causes, environmental contributions, and comorbidity should all be considered for both inclusive and exclusive purposes when evaluating someone for the FAS diagnosis (62,135). Finally, differential diagnosis for the CNS abnormalities within the FAS diagnosis is extremely difficult and should be conducted by professionals trained not only in the features of FAS, but also in the features of a broad array of birth defects and developmental disabilities so as to understand the distinguishing characteristics.

Maternal alcohol exposure. Documentation and confirmation of prenatal alcohol exposure can be extremely challenging. For birth mothers, admission of alcohol use during pregnancy can be very stigmatizing. The situation can be further complicated if the woman is still using alcohol, especially at high consumption rates. In this situation, information about alcohol use might need to be obtained from other reliable informants, such as a relative. However, the overwhelming situation encountered in the clinical setting is when a child or adult is being evaluated for FAS and little or no information about the index pregnancy is available. This frequently occurs for children in foster and adoptive homes. In this situation, every effort should be made to obtain the necessary information, but lack of confirmation of alcohol use during pregnancy should not preclude an FAS diagnosis if all other criteria are present. This would be considered "unknown prenatal alcohol exposure". In very rare instances, there will be confirmed absence of exposure. Documentation that the birth mother did not drink any amount of alcohol from conception through birth would indicate that the FAS diagnosis is not appropriate. This typically implies that the birth mother knew the date of conception (e.g., a planned pregnancy) and did not consume alcohol from that day forward, or she was prevented from drinking for some reason (e.g., incarceration). It must be noted that simple denials of alcohol use might or might not be credible and corroborating evidence should be obtained whenever possible. However, given the imprecise nature of exposure information, the following two qualifiers for prenatal alcohol exposure were suggested by the SWG:

I. **Confirmed prenatal alcohol exposure** requires documentation of the alcohol consumption patterns of the birth mother during the index pregnancy based on clinical observation; self-report; reports of heavy alcohol use during pregnancy by a reliable informant; medical records documenting positive blood alcohol levels, or alcohol treatment; or other social, legal, or medical problems related to drinking during the index pregnancy.

II. **Unknown prenatal alcohol exposure** indicates that there is neither a confirmed presence nor a confirmed absence of exposure. Examples include: the child is adopted and prenatal exposure(s) is unknown; the birth mother is an alcoholic, but confirmed evidence of exposure during pregnancy does not exist; and conflicting reports about exposure exist that cannot be reliably resolved.

CRITERIA FOR FAS DIAGNOSIS

A diagnosis of FAS requires the presence of all three of the following findings:

1. Documentation of all three facial abnormalities (smooth philtrum, thin vermillion border, and small palpebral fissures);

2. Documentation of growth deficits; and

3. Documentation of CNS abnormalities (structural, neurological or functional, or combination thereof).

It should be noted that confirmed prenatal alcohol use can strengthen the evidence for diagnosis, but is not necessary in the presence of all the previous findings. Confirmed absence of alcohol exposure would rule out the FAS diagnosis. The FAS diagnosis should be made only after ruling out other possible diagnoses associated with each criterion. A brief outline of the diagnostic criteria for FAS is presented in Table 3.

Changes in presentation of criteria across development. As would be expected for any congenital syndrome, presentation of the diagnostic features can change over development. With regards to facial features (small palpebral fissures, smooth philtrum, and thin vermillion border), it has generally been accepted that these features are most evident during infancy and the early preschool years. However, longitudinal data that specifically address this issue are not available currently. One also might expect growth parameters to change (and generally normalize) with development. This might especially be the case for children who receive nutritional or other interventions. Perhaps the criterion for which the most change over development is observed is CNS abnormalities. While structural abnormalities would remain consistent, neurological and functional deficits could resolve or change presentation at various stages of development. During the newborn and infancy periods, difficulty with arousal or behavior regulation might be observed. Slightly older infants could display delayed or abnormal motor skills. During late infancy approaching the preschool period, general cognitive developmental delay is generally reflected through delayed milestones, especially early language acquisition (note, however, that basic language skills of vocabulary and syntax generally are not areas of deficit for children with FAS). During the preschool period, attention problems and hyperactivity can emerge. In typically developing children, the late preschool through early school age (e.g., 4 through 7 years of age) is when many executive functioning and social perception skills are acquired. For example, simple planning or organization skills are learned, as well as understanding the physical and mental perspective of others. Preschoolers and school-aged children often do not fully acquire these skills. Throughout the school-age period, children with FAS can exhibit deficits or difficulty with any of the CNS domains listed in the diagnostic criteria. However, each child's pattern of strengths and weaknesses is likely to be very individualized. During adolescence and through adulthood, the pattern of deficits continues to be present and in addition, lifelong conse-

Table 3: Brief Outline of Diagnostic criteria for Fetal Alcohol Syndrome

Facial dysmorphia
Based on racial norms, individual exhibits all three characteristic facial features:

- Smooth philtrum (University of Washington Lip-Philtrum Guide rank 4 or 5)
- Thin vermillion border (University of Washington Lip-Philtrum Guide rank 4 or 5)
- Small palpebral fissures (at or below 10th percentile)

Growth problems
Confirmed prenatal or postnatal height or weight, or both, at or below the 10th percentile, documented at any one point in time (adjusted for age, sex, gestational age, and race or ethnicity).

Central Nervous System Abnormalities

I. Structural

1) Head circumference (OFC) at or below the 10th percentile adjusted for age and sex.
2) Clinically significant brain abnormalities observable through imaging.

II. Neurological

Neurological problems not due to a postnatal insult or fever, or other soft neurological signs outside normal limits.

III. Functional

Performance substantially below that expected for an individual's age, schooling, or circumstances, as evidenced by:

1. *Global cognitive or intellectual deficits representing multiple domains of deficit (or significant developmental delay in younger children) with performance below the 3rd percentile (2 standard deviations below the mean for standardized testing)*
   or
2. *Functional deficits below the 16th percentile (1 standard deviation below the mean for standardized testing) in at least three of the following domains:*
   a) cognitive or developmental deficits or discrepancies
   b) executive functioning deficits
   c) motor functioning delays
   d) problems with attention or hyperactivity
   e) social skills
   f) other, such as sensory problems, pragmatic language problems, memory deficits, etc.

Maternal Alcohol Exposure

I. Confirmed prenatal alcohol exposure
II. Unknown prenatal alcohol exposure

Criteria for FAS Diagnosis
Requires all three of the following findings:

1 Documentation of all three facial abnormalities (smooth philtrum, thin vermillion border, and small palpebral fissures);
2. Documentation of growth deficits
3. Documentation of CNS abnormality

quences of those deficits emerge, including mental health problems, inability to achieve independent living, and criminal activity (62,95,126-137).

Individuals who do not meet the full diagnostic criteria for FAS. The 1996 IOM report noted that most individuals with deficits resulting from prenatal exposure to alcohol do not express all of the features necessary to meet the criteria for an FAS diagnosis. This was confirmed in the comments of researchers, clinicians, and members of the NTFFAS/FAE during the deliberations of the SWG. Consensus has not been reached by either of these groups, or the scientific and clinical community at large regarding evidenced-based diagnostic criteria for any prenatal alcohol-related condition other than FAS. However, there is grave concern that individuals who present with the same neurodevelopmental deficits as individuals diagnosed with FAS, but who do not present with the full facial features or growth deficits, are not being afforded services because they are not given a diagnosis of FAS. Ongoing funding has been provided by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) to conduct research that might result in evidence-based diagnostic criteria for individuals with other conditions caused by prenatal alcohol use. Currently, CDC is using a collaborative database of neurodevelopmental data from five intervention studies to explore the nature of individuals who could be considered in the diagnostic category of ARND, as well as data from a prospective cohort study of 5-year-olds in Denmark. However, at this time, the only diagnostic category with scientific evidence to support clinical criteria is FAS. As future data and science are available, these guidelines can be refined and expanded to delineate other conditions resulting from prenatal alcohol exposure.

CONSIDERATIONS FOR A REFERRAL FOR AN FAS DIAGNOSTIC EVALUATION

Very often the front-line providers of services (medical, educational, or social) are faced with making the decision of whether or not to refer a child, individual, or family for a full FAS diagnostic evaluation. The SWG recognizes that this may be a difficult decision. For biological families, there may be social stigma associated with any evaluation concerning prenatal alcohol exposure. In other families, direct information about alcohol use during pregnancy may not be available or only suspected. Thus, the following guidelines were developed to provide assistance in making the referral decision, although, it is recognized that each case must be evaluated individually. Further, these guidelines were developed with the idea that when in doubt, it was preferable to refer for full evaluation by a multidisciplinary team with experience in evaluating prenatal alcohol exposure.

- For situations with known prenatal alcohol exposure: A child or individual should be referred for full FAS evaluation when there is confirmed significant prenatal alcohol use (i.e., 7 or more drinks per week or 3 or more drinks on multiple occasions, or both). If prenatal alcohol exposure in the high risk range is known in the absence of any other positive screening criteria, the primary healthcare provider should document this exposure and closely monitor the childs ongoing growth and development.

- For situations with unknown prenatal alcohol exposure: A child or individual should be referred for full FAS evaluation when:
  - there is any report of concern by a parent or caregiver (foster or adoptive parent) that his or her child has or might possibly have FAS.
  - all three facial features are present (smooth philtrum, thin vermillion border, and small palpebral fissures).

– one or more facial features are present in addition to growth deficits in height or weight, or both.
– one or more facial features are present, along with one or more CNS abnormalities.
– one or more facial features are present, along with growth deficits and one or more CNS abnormalities.

SERVICES APPROPRIATE FOR AFFECTED INDIVIDUALS AND THEIR FAMILIES

Diagnosis is never an endpoint for any individual with a developmental disability and his or her family. This is particularly true for individuals with FAS, their families, and their community. As described in the framework section, the FAS diagnosis and the diagnostic process (especially the neuropsychological assessment) are part of a continuum of care that identifies and facilitates appropriate health care, education, and community services. The learning and life skills affected by prenatal exposure vary greatly among individuals, depending on the amount of alcohol exposure and the timing and pattern of exposure, as well as each individual's current and past environment (138-139). As a result, the services needed for individuals with FAS and their families vary according to what parts of the brain have been affected, the age or level of maturation of the person, the health or functioning of the family, and the overall environment in which the person is living. Thus, service needs for any particular individual and his or her family can be quite individualistic (140).

Despite the required individualization in service needs, some general areas of service and specific services have been identified as helpful to people with FAS and their families (62). While the ideal circumstance are services and interventions that have been specifically developed for individuals with FAS and their effectiveness has been established through rigorous scientific evaluation, such programs are only now being researched and developed. Thus, most evidence for the benefit of services has been gleaned from research with other populations, clinical wisdom, and family experiences. These three sources have drawn heavily from information obtained concerning risk and protective factors that have been found through systematic research, using natural history methodology, to promote positive development or reduce the incidence of negative long-term consequences of FAS (i.e., reduce secondary conditions; 141). First, these factors will be reviewed. Then, services that are applicable to all individuals with FAS, regardless of life stage will be presented. Finally, essential services appropriate for individual life stages will be presented.

Risk and Protective factors. In a landmark study of secondary conditions for individuals with FAS, Dr. Ann Streissguth and her colleagues delineated not only the lifelong consequences of FAS, but also several basic factors that are protective or increase the risk of negative outcomes (95). This study identified many lifelong negative consequences of FAS, including disrupted school experiences, legal problems, incarceration, mental health problems, substance abuse problems, inappropriate sexual behavior, dependent living, and poor employment history. Importantly, these risks are not mutually exclusive. Any individual can (and most likely will) experience multiple risk factors that can have a cumulative effect (141). Moreover, these risks can be exacerbated by family and community expectations. Research has shown a relation between the number of risk factors encountered by an individual and poor outcomes. Reducing the number and severity of risk factors is an important step in providing services to individuals with FAS and their families. The disorder of FAS has often been described as a "hidden" disability because of the subtlety of the dysmorphia and good basic language skills (e.g., vocabulary and syntax) of many affected individuals. These factors lead to individuals with FAS being treated inappropriately because of caregivers' unrealistic

developmental expectations. FAS might be either not recognized or mislabeled as stubbornness or "bad" behavior by a caregiver, or others who encounter the affected individual (e.g., teachers, extended family, and friends). Families raising children with developmental disabilities typically report considerable parental stress related to this aspect, particularly for parents of children with FAS (62).

Several factors have been identified that can potentially reduce the odds of long-term negative outcomes in children with FAS (protective factors), including a stable and nurturing home environment during the school years, early diagnosis (before 6 years of age), absence of exposure to violence, few changes in caretaking placements, and eligibility for social and educational services. Interventions and services that maximize these protective factors while reducing risk factors will provide the best benefit to anyone with FAS and improve their chances for achieving their developmental potential (95,138).

General Needs. Helpful interventions should include those that stabilize home placement and improve parent-child interaction (138). One method for accomplishing this goal is to increase the understanding of the disorder by parents, teachers, law enforcement personnel, and other professionals who might become involved with the affected individual. Children with FAS often need unique parenting because of their difficulty with cause and effect reasoning and other executive functioning skills. Caregiver education should highlight and explain differences in the thought processes of children with FAS from typically developing children and children with other developmental disabilities. This would enable parent s to avoid potentially difficult situations (e.g., avoiding overly stimulating environments) and better manage problems when they do arise. Overall, a better functioning family that results from caregiver education promotes the stable, nurturing home that has been shown to be a positive protective factor for children with FAS (142).

Beyond the home environment, other professionals also need increased education and information concerning FAS (135). Parents can facilitate this understanding by learning to become advocates for their child. Such advocacy includes both linking families with needed community resources and making sure that the child receives maximum benefit from that service. Because the myriad of service systems is confusing and inconsistent across states, families must be educated about them at the local level. The world of social and educational services can be overwhelming, confusing, and inconsistent, and usually has a unique vocabulary that must be learned. Thus, it is important that along with a diagnosis, clinicians need to help caregivers in learning about available services, how to determine which services are appropriate for their child, and how to work productively with service providers (62).

Many prenatally exposed infants and children enter the foster or adoptive care system at an early age. A recent study estimated that the prevalence of children with FAS (or a related disorder) in the foster care system is 10 times that of the general population (143). However, while protective service agencies (PSAs) might have information about a child's prenatal history, staff members are generally not knowledgeable about FAS, do not understand the impact of the child's having FAS, or do not communicate the child's FAS status to other service systems. As a result, foster and adoptive families are most often not educated about the long-term effects and are unprepared to meet their child's needs. However, most PSAs require foster parents to take a specified number of educational courses annually. These courses should include education about the effects and developmental needs

of the child with FAS since the majority of foster parents will encounter at least one child with FAS or a related disorder during their time as a foster parent.

The assessment process is integral to a well-developed treatment plan. As has been emphasized in these guidelines, part of the diagnostic process is a comprehensive neuropsychological assessment, not only to establish CNS abnormities for the diagnosis, but also to develop the best treatment plan possible. Such a treatment plan minimizes risk factors for lifelong negative consequences and promotes protective factors that maximize developmental potential. Clinicians and s ervice providers must ensure that assessments include communication and social skills; emotional maturity; verbal and comprehension abilities; language usage; and, if appropriate, referral for medication assessments. Finally, it is the responsibility of the community at large to ensure that children with disabilities, including children with FAS, have access to and are assimilated into school, recreational, and social activities.

Age-specific services. Basic child development informs clinicians and service providers that the abilities of any one individual change dramatically at different stages of development. Intervention research informs providers that the most effective programs are those that are geared towards an individual's developmental level. There are specific "turning points" during which children demonstrate rapid and fundamental changes in their understanding of the world and in their problem-solving skills (e.g., development of object permanence or acquisition of formal operational thought). The services identified in the following sections include those for both the child and the family, grouped broadly by developmental stage. It is recognized that many of these services span beyond a single age category with considerable overlap, especially for the family.

Prenatal services. Significant development of all major organ systems occurs throughout gestation; thereby, making it imperative that women who drink during pregnancy be identified by the medical community as early as possible and be provided intervention services. Findings have indicated that children born to women who stop drinking at any point during their pregnancy have better outcomes than those who continue to drink throughout pregnancy (73). To ensure this happens, physicians, nurses, and other allied health professionals need to be trained to screen patients for possible alcohol use, to understand the detrimental effects of prenatal exposure to alcohol, to understand alcoholism as a treatable disorder, and to be familiar with treatment services. Many women who drink during pregnancy and their partners are not educated about FAS or the harmful effects of drinking during pregnancy. These prospective parents might not be prepared to address their shame or the needs of their children. Some women who experience an alcohol-exposed pregnancy might have been exposed themselves prenatally to alcohol. Therefore, treatment personnel need to be educated about both FAS and needed services to provide more appropriate treatment, as well as provide ongoing support and monitor these families closely.

Services for birth to 3 years of age. The first years of life are an important time for physical, cognitive, and emotional development. Decades of research have consistently shown the benefits of early intervention for children with developmental disabilities. Clinicians working with this age group need to familiarize themselves with the state systems that service this population. In particular, Part C of the Individuals with Disabilities Education Act (IDEA) provides early intervention for children 0 to 3 years of age . In many states, this program is administered through local health departments. A particularly appealing aspect of the Part C portion of IDEA is that FAS is considered a "presumptive eligibility" diagnosis. Presumptive diagnoses allow children "at risk" of later develop-

mental delay to be served without meeting particular eligibility criteria. That is, children who are at risk for later developmental problems can receive services, even if they test in the normal range or do not meet other eligibility criteria. This is very important for children with FAS because only about 25% score in the significantly developmentally delayed range (or the range of mental retardation for older children; 95). Referring children who have the FAS diagnosis as well as children who are exposed but do not meet the full diagnostic criteria for FAS, ensures that these children are monitored and, at appropriate ages, referred to appropriate ancillary services as needed. Many states maintain birth defects registries that track the ICD-9 code encompassing FAS (i.e., 760.71 Fetal Alcohol Syndrome) which also can facilitate such monitoring. All infants who are known to have been exposed prenatally included in these registries can be referred to the state's special child health services (note: each state will have its own name for this service) that are part of all states' maternal and child health systems. Special child health services programs provide case management and referral services for children with birth defects or developmental disabilities as well as facilitate evaluation for early intervention programs.

As noted previously, a stable and nurturing caregiving environment is a protective factor for children with FAS. Child development literature states that stable and nurturing environments promote secure attachments between infants and caregivers (144). Secure attachment facilitates emotional, social, and personality development in positive ways. Insecure or negative attachment can lead to inappropriate development in these areas, and at the most severe end of the continuum, the psychopathology of reactive attachment disorder (RAD). The time between birth and 3 years of age has been shown to be a particularly salient time for development of child and caregiver attachment. Disruption in the caregiving environment can lead to poor or negative attachment between infant and caregiver (145). Because many children with FAS are in the foster care system and experience multiple placements (due both to the nature of the system and the difficulty in parenting a child with FAS), they are at tremendous risk for negative attachment including RAD.

Services for children 3 to 6 years of age and school age. It is often during the toddler period that children with FAS will be identified and can be diagnosed. It is essential that states establish FAS diagnostic centers or ensure that their child evaluation centers have clinicians who are trained in the dysmorphic and other diagnostic criteria associated with prenatal exposure.

Following the families themselves, the educational system serves as the most constant service provider for individuals with FAS from early childhood through adolescence. Therefore, beginning with preschool programs and through secondary education, generalized essential services can be delineated. When a child reaches three years of age, early intervention services (IDEA Part C) end and families are referred to preschool handicapped programs (sometimes called special needs preschool) that are administered through IDEA Part B. Part B of IDEA differs from Part C in that there are no presumptive eligibility diagnoses. Eligibility for educational services under this program is related entirely to functional criteria and their relation to educability. As noted previously, this can make it difficult for children with FAS to qualify for these special education services because only a quarter of the children with FAS achieve standardized test scores in the range of significant developmental delay (or mental retardation), the usual eligibility threshold. However, within the IDEA framework, there are a few categories that allow children with FAS who score above the eligibility threshold to still qualify. A few children with FAS will qualify in the category of learning disabled (LD). This category is for children who demonstrate a statistically significant discrepancy (2 standard deviations or more) between overall IQ and one or more academic skills (e.g., math).

Another eligibility category that has been helpful in qualifying children with FAS is behavior disorder. However, this category should be used with care because children with FAS can learn negative behaviors from other children without receiving the benefits of a structured environment. Finally, the category of other health impaired (OHI) can be used at the discretion of the individual education plan (IEP) committee, which includes parents as well as school personnel. Services available through the school system go beyond classroom settings. Children can receive various therapies, including physical therapy (usually most appropriate for very young children), speech and language therapy, occupational therapy, or social skills training. These last two areas are particularly helpful to children with FAS because of the visual-motor deficits and problems in social interactions they encounter.

Training parents to be effective educational advocates is essential to maximize the benefits of their child's special education and to understand their child's rights. The purposes of the IEP are to insure access to appropriate habilitation and rehabilitation services (physical, occupational, speech, behavioral, mental health, and other related services) and to ensure that academic curricula are balanced with vocational training and skills of daily living (e.g., personal hygiene, money management, and family life education), when appropriate. In addition to training parents about the educational system, the preschool period, as well as elementary school years, are times when parents become more acutely aware of their child's imitations. Reinforcement and updating of information learned in early parent education settings will benefit both the child and the parents. Reviewing lessons learned will help parents adjust their expectations for the child's current functioning, as well as his or her future possibilities.

As noted previously, it is important that school staff be trained to recognize possible characteristics associated with FAS, as well as appropriate techniques for instructing students with FAS. Irrespective of whether alcohol-exposed children are in regular or handicapped preschool programs, educational methodologies need to be developed that best address their learning styles and that appropriate behavioral or mental health services are available and initiated.

Beyond services available through the educational system, families raising preschool and school-aged children continue to need services to promote positive family functioning. Such services might include behavior management training, family (or child) counseling, parenting workshops that focus on the unique aspects of parenting a child with FAS, or other types of continuing education. One service that becomes very important during these years is respite care. Such care allows a trained individual to stay with the affected child while caregivers or other family members take advantage of some time away from the child with FAS. Respite care has been shown to significantly reduce family stress and improve family functioning (146-147). Unfortunately, respite care, especially formalized and high-quality respite care, is not readily available in most communities. A clinician can help in this situation by working with the family to develop informal respite care situations, such as help from an extended family member working with the family and to provide the necessary education about FAS to such a respite care provider.

Services for adolescents. Adolescence, and even preadolescence, is one of the major turning points in the life of an individual with FAS. His or her body is changing, cognitive abilities are changing, peer groups are changing, and community expectations are changing. Because of the confusing nature of all these changes, adolescence often is the period when behavioral and mental health problems become more pronounced. Depression or anxiety, or both, can set in as the individual

struggles to cope with these changes. Increased opportunities to experience alcohol and/or drugs can lead to substance abuse problems. Families could become involved with juvenile or criminal justice systems. These are some of the most serious secondary conditions that research has identified for individuals with conditions associated with prenatal alcohol exposure (95).

It is often during adolescence that families experience high levels of stress and tension. As such, the need for individual counseling (for both child and parent), family counseling, and a strong support network becomes more crucial. However, this can be the exact stage at which agencies are reluctant to provide such services, especially if the FAS-related disability factor is not recognized. Because some amount of rebellion is expected during adolescence, the challenging behaviors of the teenager with FAS might be dismissed as transient. At the other end of the spectrum, the challenging behaviors of the adolescent with FAS can be so severe as to involve the criminal justice system.

Because adolescents will soon be leaving the safety and structure of the educational system, vocational and transitional services become essential during this stage. These services often represent a shift from academic skills and achievements to daily living skills, including employment skills. It is very important that these services be started in early adolescen ce, and not left until the individual is about to age-out of the educational system. In addition, beyond teaching the specific skills that go with a particular job, it might be necessary to explicitly teach those skills related to being a good employee (e.g., punctuality and minimized socializing). Most individuals will learn these skills through basic maturity and observational learning. Individuals with FAS often need explicit instruction as well as lifestyle supports (e.g., a job coach).

As for all adolescents, sexual behavior often becomes a critical issue during this stage. The boundaries for appropriate interaction with the opposite sex, the subtle nature of social cues, and impulse issues are difficult for any adolescent, but more so for the adolescent with FAS. Close supervision is the first line of defense during the adolescent years. However, such supervision often conflicts with the adolescent's growing desire for independence. This must be navigated with care to avoid alienating the adolescent. Also, it is probably best to be open and explicit with the teenager with FAS concerning the issues of contraception, sexually transmitted diseases, and sexual harassment. Failure to address these issues can have serious, and possibly life-threatening consequences for the affected individual, his or her family, and any children resulting from unintended pregnancies.

As mentioned previously, individuals with FAS are at high risk for involvement with the juvenile and criminal justice systems. Their lack of executive functioning skills (i.e., poor judgment), fluid language skills, and naïve social skills make them particularly vulnerable to participating in criminal activity. However, these same deficits demand that when they do encounter the justice system, their deficits should be taken into account during all aspects of justice proceedings (i.e., charges, process, punishment, and rehabilitation). As such the juvenile and criminal justice systems are major social systems in need of education regarding FAS. Special rehabilitation programs with staff that are trained to work with adolescents and young adults with FAS should be established. Such programs should be based on scientifically-based research findings that evaluate practicality as well as effectiveness.

Services for adults. In addition to all the services mentioned for the preceding age groups, adults with FAS often need support in every area of their lives. Everyday needs such as transportation issues, job assistance, housing assistance, medication reminders, money assistance, and support and

assistance when unpredicted issues arise should continue to be monitored and supported. Although not consistently available, clearly a system needs to be established that assists people with FAS in living as independently in the community as possible and includes support for housing, healthcare, and employment.

Because of federal, and often state legislation, it is very difficult for people with FAS to receive services from state developmental disability agencies, unless exposed individuals have met the eligibility criteria for services before 22 years of age. Eligibility criteria are generally based on levels of intelligence, as well as functional limitations in at least three areas associated with skills of daily living. As a result, many exposed individuals will not be eligible for services that often include an individual service plan (ISP), case management, residential and employment assistance, and possibly social security disability payments.

People with FAS might be eligible for federal assistance, such as, Medicaid, Supplemental Security Income (SSI), and Section 8 Housing subsidies, not because of their disabilities but because of their low income status. However, obtaining these services can be difficult. For example, most states have long waiting lists for Section 8 housing because of both the high demand and great need often leading to a shortage of rental units. Eligibility criteria for these services, even when based on income, should include a priority category for persons with FAS. Unfortunately, many of these housing options do not offer the support and structure that adults with FAS often need. Housing remains one of the main issues in supporting individuals with FAS for which there are no appropriate services developed or identified.

IDENTIFYING AND INTERVENING WITH WOMEN AT RISK FOR AN ALCOHOL-EXPOSED PREGNANCY

Despite ongoing efforts to inform childbearing-aged women of the risk associated with alcohol use during pregnancy, surveys conducted by the CDC and SAMHSA indicate that 9% to 12% of pregnant women in the United States report consuming alcohol and that approximately 3% report drinking at levels than have been consistently associated with adverse effects on the fetus (148-149). Also of concern are the high proportions of non pregnant childbearing-aged women whose drinking patterns exceed safe levels as defined by public health agencies (150-151). Currently more that half of all women of childbearing age (18 through 44 years of age) report alcohol use, and one in eight report binge drinking in the past month. Many of these women are sexually active and are not taking effective measures to prevent pregnancy. These women are at risk for an alcohol-exposed pregnancy in that they could have an unrecognized pregnancy and continue drinking early in pregnancy at levels that are harmful to the fetus.

One public health strategy for preventing alcohol-exposed pregnancies is to identify characteristics of women at greatest risk of having a child affected by prenatal alcohol exposure and implement prevention programs in subpopulations with higher proportions of these identified risk factors. Over the past 20 years, concerted efforts have been made to identify factors among childbearing-aged women associated with harmful patterns of alcohol consumption. One extensive review of studies reporting characteristics of women giving birth to a child with FAS found that low socioeconomic status (SES), African-American and American-Indian/Alaska-Native ethnicity, and being a smoker were characteristics commonly found among women in this group (152). Additional studies using cross-sectional survey data and special populations have extended our understanding of char-

acteristics associated with childbearing-aged women at high risk for having an alcohol-exposed pregnancy based on current drinking patterns. Factors associated with risk include being a smoker, having a low SES, being unmarried, having a history of previous or current illicit drug use, having a history of physical or sexual abuse, having psychological stress, and having mental health disorders (153-156). In an attempt to identify community-based settings that have higher proportions of preconceptional women at increased risk for an alcohol-exposed pregnancy, CDC sponsored an epidemiological study of special populations that included: women in alcohol and drug treatment centers, a large urban jail, publicly funded primary care clinics, a university-based gynecology clinic in a large urban hospital, and a cohort of women responding to a newspaper solicitation (27). Being at risk for an alcohol-exposed pregnancy correlated significantly with being (or having ever been) a smoker, having a history of inpatient treatment for drugs or alcohol, having a history of inpatient mental health treatment, having multiple sex partners, and having experienced recent physical abuse.

Primary prevention of alcohol-exposed pregnancies requires the accurate identification of women who are drinking at thresholds that have been associated with adverse pregnancy and infant outcomes before pregnancy occurs. Dietary guidelines from the U.S. Department of Health and Human Services recommend that women drink no more than one drink per day to avoid increased risk for adverse health conditions and that women who are pregnant, planning a pregnancy, or at risk of pregnancy abstain from alcohol use altogether. Research findings support these recommendations with evidence of increased risk for birth defects, spontaneous abortions, and deficits in neurocognitive development and growth at levels of seven or fewer drinks per week in some studies (157-162).

Of further concern is the pattern in which alcohol is consumed. Heavy episodic drinking, as in binge drinking, can result in increased severity of the teratogenic exposure effects because of the higher peak blood alcohol levels achieved in this pattern of consumption as opposed to lower level daily consumption (40,163). Historically, a binge episode has been considered to be five or more drinks on any one occasion, but evidence of the presence of gender effects in alcohol metabolism and higher morbidity and mortality among women than men with similar consumption patterns has prompted recommendations for defining a binge episode for women as four or more drinks on any one occasion or on any one day. Current recommendations on clinical thresholds published by the NIAAA are that women drinking more than seven drinks per week or more than three drinks on any given day in the past month be further assessed for risk of developing alcohol-related problems. As stated earlier, pregnant women are advised to abstain from alcohol use. This is a long-standing federal advisory and one supported by major professional societies as well (9,164).

Measurement of current alcohol consumption can be enhanced through the use of reliable screening and assessment methods. A number of screening instruments have been developed that offer the practitioner options for clinical assessment of childbearing-aged women. When selecting a screening tool for routine implementation, healthcare professionals should consider factors such as the goals of the screening process, the target population, and the ease of administration. All women of childbearing age should be screened for alcohol use, including women who are pregnant or nursing, women who are planning a pregnancy, and women who are sexually active and not using contraception (such as teens and college-aged women).

Methods and Considerations for Establishing Reliable Estimates of Alcohol Use. Measures most commonly used in alcohol assessment include items that address quantity, frequency, and pattern (variability) of drinking. Quantity-frequency measures (QF) inquire about average or typical consumption patterns. The simplest measures assess the amount of drinking on average drinking days (Q), and the average number of days on which alcohol is consumed (F). QF measures can be used to estimate a woman's average number of drinks per day or the amount of absolute alcohol consumed per day (AA score). To assess for binge drinking, some investigators have recommended that screening questions should include measures of maximum quantity consumption and frequency of maximum quantity consumption (165). *Helping Patients with Alcohol Problems: A Practioner's Guide,* developed by the NIAAA, (166) recommends quantity-frequency and maximum quantity questions as the primary screening test. These questions have been shown to have relatively high sensitivity and specificity, are easy to use, and can be incorporated into a health practice with minimal cost and effort (167).

Additional considerations for alcohol screening include measurement of the types of alcoholic beverages the woman consumes. The development of new ways of marketing wine and beer, including higher alcohol concentration malt liquors and beer in 20- to 45-ounce containers, has increased the need to provide women who drink with more specific standards to estimate their consumption. Studies show that reliance on standard drink measurements when assessing drinking practices of heavier drinkers or those consuming higher alcohol content beverages can result in considerable underestimation of alcohol consumption (168-169). Moreover, beverage-specific questions have been shown to be more accurate than grouped beverage questions (170).

One of the most reliable assessment tools for gathering accurate self-reported alcohol use is the timeline follow back (TLFB) measure (171). This method of alcohol use assessment typically asks respondents to think back over the past 90 days and report daily drinking amounts during that period of time. Respondents are given a calendar and asked to identify special events that occurred during that time period, such as parties, birthdays, or holidays that might serve to trigger recall of drinking occasions. A major strength of the TLFB measure is its ability to capture both average daily drinking and sporadic drinking that might entail drinking at higher levels of consumption. Because of the time requirements necessary for gathering information using the TLFB approach, it is not easy to use in primary care settings but it has been used in clinical research to establish the reliability and validity of other briefer screening and assessment tools (172).

Screening Tools. Several brief questionnaires have been developed over time to screen for problematic alcohol use in adults in diverse populations and settings. Screening tools currently in use include the CAGE, AUDIT, T-ACE, TWEAK, MAST, S-MAST, NET, RAPS4, and RAPS4-QF (173). The CAGE (174)is a four-item alcohol use measure designed to detect alcoholism and is one of the most commonly used screening instruments for men and women. The four questions ask the respondent: (C) Have you ever felt you should CUT down on your drinking? (A) Have people ever ANNOYED you by criticizing your drinking? (G) Have you ever felt bad or GUILTY about your drinking? and (E) Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (EYE OPENER)? Each item is scored as a 0 (no) or 1 (yes) and scores of 2 or greater are considered clinically significant.

The AUDIT is a 10-item self-report questionnaire developed by the world health organization (WHO) for identifying individuals whose alcohol consumption has become hazardous or harmful

to their health (175). The items on the AUDIT are constructed to measure frequency of alcohol consumption, dependence symptoms, and the personal and social consequences of drinking. The first three questions of the AUDIT address the quantity, frequency, and maximum amount of alcohol consumed. The remainder of the questionnaire has two items from the CAGE, (feelings of guilt about drinking and the need for a drink first thing in the morning after a heavy drinking session—eye-opener) in addition to questions on the frequency of being unable to stop drinking once drinking starts, frequency of being unable to do what is normally expected because of alcohol use, frequency of memory loss of the previous night due to drinking, frequency of injury to self or others as a result of drinking, and frequency of others expressing concern over the individual's drinking (a relative, friend, or doctor). A score of eight or more is considered significant for high-risk consumption. The measure has good psychometric properties and has an advantage over other screening tools in that it measures not only experienced consequences of drinking, but also whether an individual is currently drinking at levels likely to eventually result in problems (176). The instrument has been used and validated in cross-cultural populations (177). One review of 38 studies on screening for alcohol problems in women and men in primary care settings found the AUDIT was more effective in identifying individuals with at-risk, hazardous, or harmful drinking patterns, while the CAGE proved superior in detecting alcohol abuse and dependence (178). Another study of women who were receiving outpatient care through the Veterans' Administration found that the AUDIT-C (comprised of the first three items of the AUDIT on quantity, frequency, and maximum drinks per drinking occasion) proved to be more sensitive than the full 10-item AUDIT (179). Such findings suggest that when time of administration is a consideration, the shorter AUDIT-C might be used as the screener of choice.

Two screening tools that have been specifically developed and used with pregnant women are the T-ACE and the TWEAK (180-183). The T-ACE has four questions that take less than a minute to ask. The questions are: (**T**) TOLERANCE, how many drinks does it take to make you feel high? (**A**) Have people ANNOYED you by criticizing your drinking? (**C**) Have you ever felt you ought to CUT DOWN on your drinking? (**E**) EYE OPENER, Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? One point is given for each affirmative answer to the **A, C, E** questions, two points when a pregnant woman reports a tolerance of more than two drinks to feel high. A positive screen is a score of two or more points. The T-ACE has been shown to be an efficient screen for risk drinking in pregnant women and out-performs medical staff assessment alone (184). Its brevity (four-items) is an important asset and increases its utility for clinical practice.

Like the T-ACE, the TWEAK attempts to elicit information on the following: (**T**) TOLERANCE for alcohol; (**W**) WORRY or concern by family or friends about drinking behavior; (**E**) EYE OPENER, the need to have a drink in the morning; (**A**) "blackouts" or AMNESIA while drinking; and (**K**) the self-perception of the need to CUT DOWN on alcohol use. Scores range from zero to seven. The tolerance and worry questions each contribute two points and the other three questions contribute one point each. Any endorsement of the worry question is scored a two. On the tolerance question, if three or more drinks are needed to feel high, the question is scored as a two. Other versions of the tolerance question ask: How many drinks does it take before the alcohol makes you fall asleep or pass out? Or, if you never drink till you pass out, what is the largest number of drinks you have or can hold? These questions are scored as a two if the woman answers five or more drinks. Using these questions, however, results in lower sensitivity and specificity. A total score of three or more on the TWEAK is suggestive of harmful drinking pat terns (185).

Studies assessing the relative effectiveness of various screening tools have yielded different findings depending on the populations studied. Bradley et al. (186) summarized data from 13 published, peer-reviewed articles that contained information on the performance of alcohol screening questionnaires with non pregnant women and with obstetric patients during the periconceptional period. The results revealed that, for non pregnant women, the CAGE had low sensitivity in predominantly White female populations, but was a reasonable choice for identifying past year or lifetime alcohol dependence in predominantly African American female populations. Overall, the five-item TWEAK appeared to be the optimal screening questionnaire for identifying heavy drinking or alcohol abuse and dependence in racially mixed populations of non pregnant and pregnant women.

Some clinicians have suggested that the use of screeners best suited for identifying high-risk heavy drinkers might not be optimal for identifying pregnant women with irregular or lighter patterns of consumption that might still pose a risk for fetal development. Using confidential reporting procedures, one study examined the effectiveness of the TWEAK for assessing any report of drinking following pregnancy recognition in a group of low-income pregnant women participating in WIC (187). With a cut point score of two or greater, the specificity of the TWEAK was high for all ethnic groups studied; however sensitivity, while high for White non-Hispanic women, was low for African-American non-Hispanic and Hispanic women. Because any endorsement of alcohol use was sufficient for classification as a drinker in this sample, low sensitivity on the TWEAK might have been due to the fact that women were drinking at levels that were too low to result in alcohol-related problems but, were still high enough to be detrimental to the developing fetus. From a practical standpoint, the high specificity of the TWEAK supports its utility in busy clinic settings. High specificity suggests the TWEAK is effective in screening women who are not high risk, and as shown in the study cited previously, women who report not drinking at all. Nevertheless, the fact that the TWEAK had variable sensitivity for women from different ethnic backgrounds suggests that additional methods of screening should be employed in order to increase the detection of women who might need intervention.

Drinking among adolescents and college students has long been recognized as a significant problem with far-reaching public health implications (188-189). Although the most problematic drinking in adolescence has been documented among males when compared to females, alcohol use in females has been associated with decreased use of contraception (increasing the likelihood of an unintended pregnancy), increased sexual assault, and more sexually transmitted diseases. Because of these significant negative health consequences, the American Medical Association Guidelines for Adolescent Preventive Services recommend screening of adolescents for alcohol and other drug use as part of routine medical care (190). To effectively screen adolescents, the ideal screening tool must be developmentally appropriate and practical for use in busy medical offices or clinics. Although the CAGE and the AUDIT are relatively brief, their developmental appropriateness is questionable. Indeed, current research suggests that the CAGE is not appropriate for screening adolescents and that a much lower cut point of two (rather than the eight recommended for adults) on the AUDIT is optimal for identifying alcohol use problems in this population (191).

Several measures have been developed specifically for use with adolescents, such as the Rutgers Alcohol Problem Index (192) and the College Alcohol Problem Scale (193); however, these tools might not be practical for universal screening. One brief screening device, the CRAFFT, developed for adolescents, is simple to score, inquires about alcohol and drug use, and was found to have good psychometric properties in a sample of predominately female youths 14 through 18 years of age

(194). CRAFFT is an acronym for the first letters of key words in the test's six questions: (**C**) Have you ever ridden in a CAR driven by someone (including yourself) who was high or had been using alcohol or drugs? (**R**) Do you ever use alcohol or drugs to RELAX, feel better about yourself, or fit in? (**A**) Do you ever use alcohol or drugs while you are by yourself, ALONE? (**F**) Do you ever FORGET things you did while using alcohol or drugs? (**F**) Does your family or FRIENDS ever tell you that you should cut down on your drinking or drug use? (**T**) Have you ever gotten into TROUBLE while you were using alcohol or drugs? Each question on the CRAFFT is given a score of one and a cut point of two provides moderate sensitivity (.70) and excellent specificity (.94) for identifying alcohol use disorders in adolescents. The authors CRAFFT recommend that any positive answer on this measure be followed by further assessment of quantity, frequency, and pattern of use to increase sensitivity and to guide decisions about the need for intervention.

A number of studies have shown a strong association between alcohol intoxication and trauma (195). The Trauma Questionnaire was developed to screen patients in an unobtrusive way without asking them directly about their alcohol use (196). The questionnaire consists of four questions asking about injuries in the last five years (fractures or dislocations of bones or joints, traffic accidents, head injury, or injury during a fight or assault). The questionnaire has been shown to have high sensitivity and specificity for identifying high-risk alcohol use and to be acceptable to respondents and physicians.

Computer-Assisted Interviews and Laboratory Screening Measures. The method of delivery of questions about alcohol use has been shown to influence truthful reporting. Clinical interviews might not be as effective in eliciting truthful responses from women because practitioners are not always comfortable asking these questions in a face-to-face interview. Moreover, women could underestimate their alcohol use because of reluctance to discuss this potentially sensitive subject. For this reason, self-administered questionnaires might improve the validity of self-report.

The Audio Computerized Self-Report Interview has been successfully used in prenatal clinics serving disadvantaged low-literacy minority women (197). Questions asked by a recorded voice through earphones are drawn from the TWEAK with quantity and frequency questions pertaining to three months before and during pregnancy are included. Acceptability studies have revealed that patients liked this method of screening.

Laboratory screening measures offer promise for obtaining objective evidence of problem drinking (198-199). The most common biomarkers are gamma glutamyltransferase (GGT) and carbohydrate-deficient transferring (CDT). Fatty acid ethyl esters synthase (FAEE) can be found in the hair of alcohol using women. This biomarker could hold promise for screening for alcohol use in pregnant women, although the dynamics of enzyme expression appear to be complex and changes occur only at high alcohol doses. Low sensitivity in non alcoholic women and the high cost of laboratory analysis make these measures less feasible for use in more universal screening.

Brief Intervention. Brief intervention (BI) has been shown to be a low-cost, effective treatment alternative for alcohol problems that uses time-limited, self-help, and preventative strategies to promote reductions in alcohol use in nondependent individuals, and in the case of dependent people, to facilitate their referral to specialized treatment programs (200-203). Overall, BI for alcohol problems has been shown to be more effective than no intervention and often as effective as more extensive intervention (204). Effective prevention programs frequently employ a multicomponent

approach combining cognitive-behavioral techniques with norms clarification, education, and motivational enhancement interventions. BI is usually restricted to fewer than four sessions and is typically performed in a treatment setting that is not specific for alcoholism. It is often performed by personnel who are not specialists in the treatment of alcohol use and abuse, and is provided to individuals at varying levels of risk for negative consequences because of drinking, rather than those who are considered alcohol dependent (205).

Six elements characterize the key ingredients of standardized brief intervention summarized by the acronym FRAMES (206). These are: **F**eedback of personal risk, **R**esponsibility for personal control, **A**dvice to change, **M**enu of ways to reduce or stop drinking, **E**mpathetic counseling style, and **S**elf-efficacy or optimism about cutting down or stopping drinking. The intervention also involves establishing a drinking goal in the form of a signed contract and follow up of progress with ongoing support. Studies reveal that supportive, nonjudgmental techniques in which trained personnel counsel women can lead to decreased alcohol consumption during pregnancy. The most effective intervention approaches avoid the use of moral or volitional injunctions and instead focus on reduction of alcohol use without criticism or provocation of guilt (205). Effective interviewers have been found to have a thorough knowledge of the intervention technique, an optimistic attitude about change, a compassionate style, genuineness and respect for clients, an ability to avoid arguments that evoke patient defensiveness, and comfort discussing alcohol problems (207-208).

Motivational Interviewing. A technique often used in brief interventions is motivational interviewing (MI). MI uses an empathic , client-centered counseling approach to increase readiness for change by resolving ambivalence about behavior change (207). The process explores the client's ambivalence in an atmosphere of acceptance, warmth, and positive regard. Although the session is structured and to the point, direct persuasion and coercion are avoided. The goal is to enhance the discrepancy between the reasons for changing versus staying the same. More than 24 studies of MI have found beneficial effects in decreasing problem drinking and other health-related problem behaviors (209).

Manualized Brief Intervention. Although the findings of the previously cited studies provide the foundation for intervention and prevention efforts, the usefulness of MI in a busy clinic or medical practice might be limited in that it requires additional training and clinical skills development. Recently, standardized manualized BI techniques to reduce alcohol consumption have been developed. One such intervention is Project CHOICES (Changing High-risk alcohol use and Increasing Contraception Effectiveness Study), which is funded by CDC. Project CHOICES is an example of a brief intervention using motivational interviewing techniques aimed at preventing alcohol-exposed pregnancies among high-risk women in various community settings (210). This project focused on both alcohol risk reduction and pregnancy postponement until alcohol use was decreased in a group of non pregnant women who were of childbearing age, fertile, sexually active, and using ineffective or no contraception. Phase I results revealed that at six-month follow up, 68.5% of the women were no longer at risk of having an alcohol-exposed pregnancy, 12.6% had reduced their drinking only, 23.1% reported using effective contraception only, and 32.9% reported doing both. A Phase II randomized controlled trial is currently underway testing the efficacy of this approach and is slated for completion in fall 2004. Another recent CDC-funded study still underway is Project Balance, which uses a briefer adaptation of Project CHOICES and is aimed at female college students, encouraging them to abstain from alcohol or to use contraception if they drink.

Four randomized controlled studies, funded by NIAAA, serve as further examples of the utility and effectiveness of this approach. These studies included women of different socioeconomic and cultural backgrounds and were conducted in doctors' offices and community settings. Two of the studies found that manualized BI was successful in decreasing alcohol use during subsequent pregnancies in high-risk women, thus preventing possible negative developmental sequelae in their offspring (211). The other two studies, one working with high-risk, White, middle class pregnant women in physicians' offices and one working in WIC community clinics with primarily low risk, low-income Hispanic clients, also found manualized BI to be a promising approach (212-214). In the WIC study, better infant outcomes were reported, including longer birth lengths and a lower infant mortality rate. Significantly, in both studies, the control conditions that included an assessment of alcohol consumption and simple advice to stop or cut down on drinking were almost as effective as the manualized BI itself. The success of these projects in reducing alcohol consumption in both experimental and control groups was postulated to be due to the desire of pregnant women to have healthy pregnancies and to the time and attention that interventionists provided for women in both groups.

Computerized Brief Intervention One recently developed study is investigating the use of a computerized method of a BI that incorporates the use of vessel size and normative education that allows a woman to evaluate her own consumption levels (169). Once a woman has been educated about her consumption levels, she then participates in a standardized BI. This approach is promising in that it incorporates many recommended aspects of screening, educating, and assisting women in recognizing that they might have a drinking problem, and then providing a brief intervention. The automated computerized assessment is designed for use in prenatal clinics and is currently being tested at a large HMO through an NIAAA grant. Although the effectiveness of this intervention has yet to be validated, it offers a potentially useful method that could be expanded nationally.

Improving Use of Screening and Brief Intervention Technology by Clinicians. Research devoted to finding ways to encourage clinicians to use brief interventions indicates that routine educational approaches might not be effective. Effective strategies include (1) conducting educational programs at the intervention site; (2) using specific step -by-step, evidence-based clinical protocols; (3) using skills-based role playing; (4) holding peer group discussions; and (5) using a credible expert trainer or educator. Brevity, repetition, and reinforcement of recommended practices are also key program elements (215). In an effort to enhance physician uptake of current screening and intervention approaches for preventing alcohol-exposed pregnancies, the NIAAA and the Office of Research on Minority Health recently collaborated in the development of a guide for primary care providers for screening pregnant and non pregnant women on selected health behaviors, including alcohol use, and recommendations for appropriate advice depending on the level of alcohol use and consequences (166). More recently, CDC funded four regional training centers on FAS to provide education and training to medical and allied health professionals and students about identification and diagnosis of children affected by prenatal alcohol exposure and effective approaches for intervening with and preventing these conditions. More information about these and other resources can be found by accessing the websites provided at the end of this section.

Universal screening for alcohol use should be conducted among all women of childbearing age. Screening can be done in both physicians' offices and in community health settings. Simple screening techniques that include measures of quantity, frequency, and heavy episodic drinking, as well as

behavioral manifestations of risk drinking, have proven to be most beneficial. For non pregnant women, the AUDIT, TWEAK, and CAGE have been found to be useful screening tools depending on the population characteristics of the community as described in the studies reviewed earlier. However, studies on gender-specific modifications of these screening tools have been recommended because women report increased psychosocial problems at lower levels of consumption than men. Based on some empirical evidence, reduced cut points for women have been recommended, including a cut point of 4 or more for the AUDIT, 2 or more for the TWEAK, and 1 or more for the CAGE (186). For pregnant women, the T-ACE and the TWEAK are the recommended screening tools of choice. The CRAFFT shows promise as an alcohol and other drug screener for female adolescents. Findings support better identification when screening instruments are used versus clinical assessment alone. Brief interventions administered by physicians and allied health professionals in medical and non medical settings are effective in bringing about reductions in drinking.

Women who are pregnant, planning a pregnancy, or at risk of pregnancy should be advised not to drink, as no safe threshold of alcohol use during pregnancy has been established. Non pregnant childbearing-aged women should be advised to drink no more than seven drinks per week and no more than three drinks on any one occasion.

Both BI approaches and MI techniques have been found to be efficacious with pregnant and non pregnant women in promoting reduction in alcohol consumption. Furthermore, some evidence suggests pregnant women are motivated to stop drinking even if the intervention includes only an assessment of alcohol use with simple advice to stop or reduce drinking. Research also indicates that interventions are effective with pregnant women who are light as well as high-risk drinkers. Moreover, preconceptional counseling of women of childbearing age who are at risk for an alcohol-exposed pregnancy and who are not using effective contraception has been demonstrated as a promising method of prevention as well as computerized versions of standardized methods of intervention. This year the U.S. Preventive Services Task Force released recommendations calling for use of the screening and behavioral counseling interventions for adults in primary care setting, including pregnant women (216-217). These evidence-based recommendations mirror the content of these guidelines with respect to the specific types of screening tools recommended and the components of effective brief interventions to be used. The recommendations of the U.S. Preventive Services Task Force, which is supported by the federal Agency for Healthcare Research and Quality, provide further support for the need for widespread public health implementations of these prevention technologies to reduce the harmful consequences of alcohol misuse, including FAS and other prenatal alcohol-related conditions. Information about reported and other federally sponsored studies in FAS and prenatal alcohol screening and intervention can be obtained at the following websites: www.nih.gov; www.cdc.gov; www.samhsa.gov; and www.preventiveservices.ahrq.gov.

SUMMARY AND FUTURE STEPS

In 2002, CDC was congressionally mandated to develop diagnostic guidelines for FAS and other prenatal alcohol-related disorders and integrate them into medical and allied health education.

With input from a SWG composed of clinicians, experts, and families, and from the NTFFAS/FAE, scientific and clinical evidence was reviewed to develop guidelines that offer a balance between conservative and overly inclusive definitions of FAS. Criteria for conditions not meeting the clinical definition of FAS (e.g., ARND) were not established because scientific evidence is insufficient at this time. Clinical and scientific research on FAS and those conditions resulting from prenatal alcohol exposure that do not meet the criteria for an FAS diagnosis is currently underway. These findings and advances will contribute to further refinement of the FAS criteria, and could potentially delineate additional diagnostic categories and criteria for conditions other than FAS. The development of these FAS guidelines is a continuous process. Efforts to develop and refine other diagnostic categories to identify FAS and related conditions need to continue.

During this guidelines development process, several key issues emerged that deserve mention.

1. More information on the neurodevelopmental effects of prenatal exposure to alcohol is needed. Particular emphasis should be placed on finding the unique aspects of FAS that will help differentiate it from other birth defects or developmental disabilities, or both.

2. Efforts to improve the clinical assessment tools (e.g., facial and growth measures) used to diagnose FAS should continue, particularly in terms of racial and ethnic variations and age.

3. All children should be screened for the possibility of an FAS diagnosis. As physicians and other allied health professionals become educated about this disorder, screening for FAS should become routine.

4. Better communication between obstetricians, gynecologists, and pediatricians is needed to improve documentation on prenatal alcohol use. This would help with the diagnosis of prenatal alcohol exposure in the child and could help identify women at risk for future alcohol-exposed pregnancies.

5. Service agencies must provide a way to qualify children with FAS and related disorders who do not meet their traditional eligibility requirements.

6. Further research and resources are needed to identify and treat women at risk for an alcohol-exposed pregnancy.

7. Awareness, both in the public and professional arenas, about the dangers of drinking alcohol during pregnancy and about FAS and how the condition affects children and their families is essential. A key avenue to avoiding FAS is active promotion of programs to increase awareness of the dangers of drinking alcohol during pregnancy and promotion of prevention activities that increase understanding of the risks of alcohol as well as the risks for an alcohol-exposed pregnancy.

Over 30 years ago, researchers first described FAS . Much has been learned about the disorder since that time, as is reflected in these guidelines. However, there is still much more to learn about the entire spectrum of effects from prenatal alcohol exposure. Future work will address these gaps. To reduce FAS and other prenatal alcohol-related conditions, the key is prevention. Federal, state, and local agencies; clinicians and researchers; educational and social service professionals; and families

need to work together to educate women of childbearing age and communities across the country about the risks of drinking alcohol during pregnancy.

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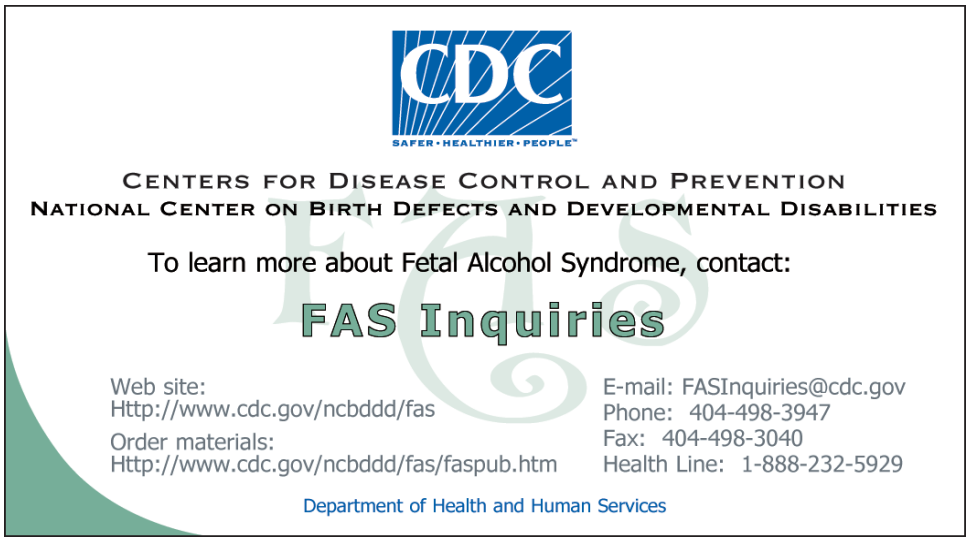
Notes

Notes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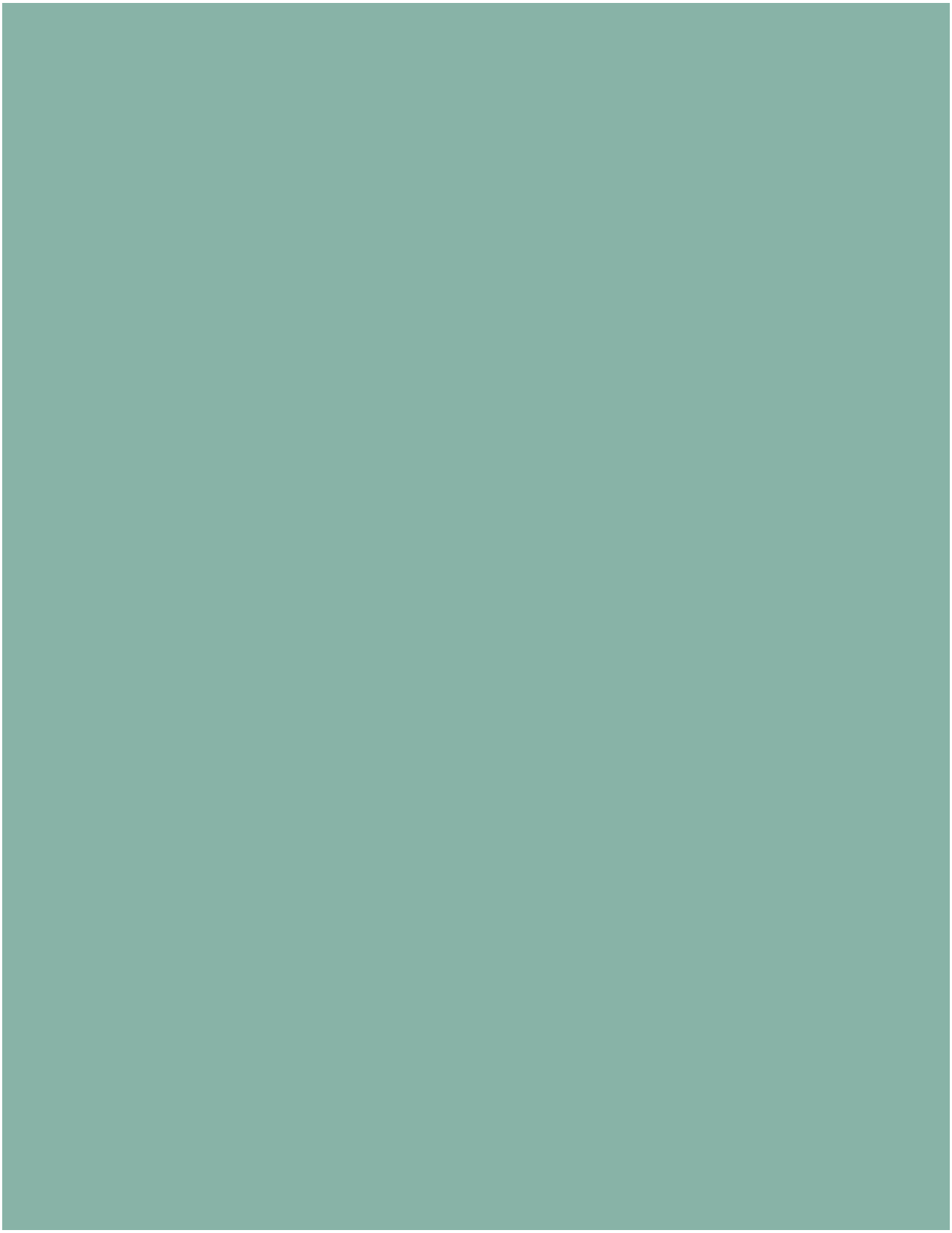

ARTICLE

Comparison of the 4-Digit Diagnostic Code and the Hoyme Diagnostic Guidelines for Fetal Alcohol Spectrum Disorders

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ABSTRACT

OBJECTIVE. The 4-Digit Diagnostic Code for fetal alcohol spectrum disorders and the Hoyme fetal alcohol spectrum disorders diagnostic guidelines differ markedly. The performances of the 2 diagnostic systems were compared.

METHODS. The fetal alcohol syndrome diagnostic criteria from the 4-Digit Code and Hoyme guidelines were applied to 952 patients who had received an interdisciplinary, fetal alcohol spectrum disorders, diagnostic evaluation at the University of Washington with the 4-Digit Diagnostic Code and 16 children with confirmed absence of prenatal alcohol exposure.

RESULTS. The prevalence of fetal alcohol syndrome was 3.7% with the 4-Digit Code and 4.1% with the Hoyme guidelines. Although the prevalences were similar, the patients identified were not. Only 17 individuals met the fetal alcohol syndrome criteria for both systems. An extraordinary number of patients (35%) met the Hoyme criteria for the fetal alcohol syndrome facial phenotype, but only 39 of those 330 patients met the Hoyme criteria for fetal alcohol syndrome. Even some children with no alcohol exposure (25%) had the Hoyme fetal alcohol syndrome face. The specificities of the Hoyme fetal alcohol syndrome face for the Hoyme fetal alcohol syndrome diagnosis and prenatal alcohol exposure were low in these populations.

CONCLUSIONS. Without a specific facial phenotype, a valid diagnosis of fetal alcohol syndrome cannot be rendered for patients with prenatal alcohol exposure, because a causal link between their outcomes and exposure cannot be established, and a valid diagnosis of fetal alcohol syndrome cannot be rendered for patients with unknown alcohol exposure, because the face cannot serve as a valid proxy measure for alcohol exposure. Diagnostic guidelines must confirm the specificity of their fetal alcohol syndrome facial criteria to validate their diagnostic criteria.

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Key Words
diagnostic methods, fetal alcohol syndrome, fetal alcohol spectrum disorders, evaluation, guidelines

Abbreviations
FASD—fetal alcohol spectrum disorders
FAS—fetal alcohol syndrome
OFC—occipital frontal circumference
PFL—palpebral fissure length
IOM—Institute of Medicine
CDC—Centers for Disease Control and Prevention
ARND—alcohol-related neurodevelopmental disorder
ARBD—alcohol-related birth defects
CNS—central nervous system
DPN—Diagnostic and Prevention Network
CI—confidence interval

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FETAL ALCOHOL SPECTRUM disorders (FASD) is a general term used to describe the full spectrum of adverse outcomes observed among individuals with prenatal alcohol exposure. Fetal alcohol syndrome (FAS) and partial FAS are 2 of several medical diagnoses that fall under the designation of FASD. In the past 10 years, several diagnostic guidelines for FASD have been published, including the Institute of Medicine (IOM) FASD guidelines in 1996,[1] the FASD 4-Digit Diagnostic Code (Fig 1) in 1997, 1999, and 2004,[2–5] the Centers for Disease Control and Prevention (CDC) FAS guidelines in 2004,[6] the Canadian FASD guidelines in 2005,[7] and the Hoyme FASD guidelines in 2005.[8] An interdisciplinary approach to diagnosis, with a more case-defined approach, as proposed originally by Astley and Clarren and colleagues,[4,9,10] was adopted in principal in all subsequent guidelines. Key contrasts do exist, however (Table 1). Of all guidelines published after the 4-Digit Code, the Canadian guidelines are most similar to the 4-Digit Code. Both systems cover the full spectrum of diagnostic outcomes and adhere to strict criteria that use the standard medical statistical definition of "abnormal" as ≥2 SDs below the mean or its equivalent, ≤2.5th percentile. The criteria used by the 2 systems to define each diagnosis under the designation of FASD are nearly identical.

In contrast to the 4-Digit Code and Canadian guidelines, the CDC guidelines address only FAS and have more-relaxed facial and central nervous system (CNS) criteria, using diagnostic cutoff values of ≥1 SD below the mean or ≤10th percentile. By definition, the 10th percentile and −1 SD are both within the normal range. One standard deviation below the mean is equivalent to the 16th percentile. The 10th percentile is equivalent to 1.3 SDs below the mean.

The Hoyme guidelines, while addressing the full spectrum of outcomes, diverge considerably from the 4-Digit Code, the CDC guidelines, and the Canadian guidelines. For the diagnosis of FAS, the Hoyme guidelines further relax the facial criteria, requiring only 2 of the 3 diagnostic features specified by the CDC; restrict the CNS criteria to structural abnormalities only; and relax the criterion for small head circumference from the medical definition of microcephaly (≤2.5th percentile) to ≤10th percentile. Hoyme et al[8] referred to their FASD diagnostic guidelines as a clarification of the 1996 IOM criteria. The 2 sets of guidelines are authored by separate groups, however.

All 4 sets of guidelines require prenatal alcohol exposure to be confirmed but allow a diagnosis of FAS to be rendered if prenatal alcohol exposure is unknown. The Hoyme guidelines go farther by requiring that the confirmed exposure be excessive. The 4-Digit Code does not require confirmation of excessive exposure because (1) there is no known threshold of exposure below which all fetuses are not at risk for FAS; (2) requiring excessive exposure may send an unsafe message that only high levels of alcohol use are damaging to the fetus; and (3) it is rarely, if ever, possible to confirm the accuracy of the quantity, frequency, and timing of exposure reported to a diagnostic clinic. There are many potential threats to the reliability of a prenatal alcohol exposure history. Birth mothers may be reluctant to report that they drank during pregnancy. They may be unable to recall accurately how much they drank, because the child's diagnostic evaluation is often conducted several years after the pregnancy. Furthermore, frequently the birth mother is not present at the time of the child's diagnostic evaluation. Eighty-one percent of children diagnosed at Washington State FAS Diagnostic and Prevention Network (DPN) clinics are in foster or adoptive care; therefore, information on maternal alcohol exposure is obtained frequently from indirect sources. The 4-Digit Code has demonstrated, however, that rendering a diagnosis of FAS, as defined by the 4-Digit Code, when alcohol exposure is unknown is medically valid. This is because the rank 4 FAS facial phenotype (Fig 2), as defined by the 4-Digit Code, is so specific to FAS (99.8%)[11–14] that it serves as a valid proxy measure of prenatal alcohol exposure. The sensitivity (100%) and specificity (99.8%) of the rank 4 FAS facial phenotype to the 4-Digit diagnosis of FAS have been derived from properly designed split-half empirical studies[12,13] and validated through population-based screening and surveillance programs.[11,14] As the FAS facial criteria are relaxed,

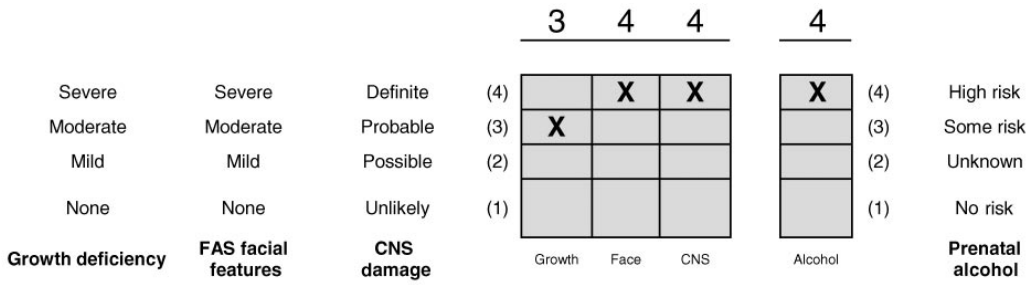


FIGURE 1
Four-Digit Diagnostic Code grid. The 4-Digit Code (3444) that is inserted in the grid is 1 of 12 codes that meet the diagnostic criteria for FAS.[5]

TABLE 1 Comparison of Key FAS Diagnostic Criteria Across 5 FASD Diagnostic Guidelines

	IOM (1996)	4-Digit Code (2004)	CDC (2004)	Canadian (2005)	Hoyme (2005)
Growth	At least 1 of the following: low weight for height, low birth weight, or decelerating weight	Prenatal or postnatal height or weight of ≤10th percentile (growth ranks 2, 3, or 4)	Prenatal or postnatal height or weight of ≤10th percentile	At least 1 of the following: prenatal or postnatal height or weight of ≤10th percentile or low weight-to-height ratio (10th percentile)	Prenatal or postnatal height or weight of ≤10th percentile
Face	Characteristic pattern that includes features such as short PFL, flat upper lip, flattened philtrum, and flat midface	All 3 of the following (facial rank 4; Fig 3): PFL of ≤3rd percentile, philtrum rank 4 or 5, and lip rank 4 or 5	All 3 of the following: PFL of ≤10th percentile, philtrum rank 4 or 5, and lip rank 4 or 5	All 3 of the following: PFL of ≤3rd percentile, philtrum rank 4 or 5, and lip rank 4 or 5	Two of the following 3: PFL of ≤10th percentile, philtrum rank 4 or 5, and lip rank 4 or 5
CNS	At least 1 of the following: OFC of ≤3rd percentile (microcephaly), abnormal structure, or hard/soft signs	At least 1 of the following (brain rank 3 or 4): OFC of ≤3rd percentile (microcephaly), abnormal structure, seizure disorder, hard signs, ≥3 domains with impairment ≥2 SDs below the mean (domains may include but are not limited to cognition, memory, language, executive functioning, and attention-deficit/hyperactivity disorder), or global deficits	At least 1 of the following: OFC of ≤10th percentile, abnormal structure, seizure disorder, hard/soft signs, ≥3 domains (cognitive or developmental, executive functioning, motor, attention-deficit/hyperactivity disorder, social, or other) with impairment ≥1 SD below the mean, or global deficits	Impairment[a] in ≥3 of the following domains: hard/soft signs, structure, cognition, communication, academic achievement, memory, executive functioning, abstract reasoning, attention-deficit/hyperactivity disorder, adaptive behavior, social skills, and social communication	At least 1 of the following: OFC of ≤10th percentile or abnormal structure
Alcohol	Confirmed or unknown	Confirmed (alcohol rank 3 or 4) or unknown (alcohol rank 2)	Confirmed or unknown	Confirmed or unknown	Confirmed to be excessive or unknown

[a] Impairment indicates scores ≥2 SDs below the mean, discrepancies of 1.5 to 2 SDs among subtests, or ≥1 SD discrepancy between subdomains.

their sensitivity and specificity for FAS decrease markedly. Neither the CDC guidelines nor the Hoyme guidelines assessed or reported the sensitivity or specificity of their relaxed criteria for the FAS facial phenotype as their criteria for a FAS diagnosis.

The Hoyme diagnostic criteria for FAS also differ from the 4-Digit Code, CDC guidelines, and Canadian guidelines in that the diagnosis is based solely on physical features of growth, facial anomalies, and structural brain abnormalities. Therefore, an interdisciplinary clinical team (eg, psychologist, occupational therapist, and speech/language pathologist) would have no role in the derivation of a FAS diagnosis. Typically, the most disabling feature of FAS is the cognitive/behavioral impairment. With the Hoyme guidelines, a child would meet the CNS criteria for FAS by having nothing more than an occipital frontal circumference (OFC) in the 10th percentile, even in the presence of normal or above-normal cognitive/behavioral function. An OFC in the 10th percentile does not meet the medical definition of microcephaly (≤2.5th percentile). By definition, 10% of the general population has an OFC of ≤10th percentile. In contrast, a child who presents with severe mental retardation (IQ of 55) but no evidence of structural brain abnormalities would fail to meet the Hoyme diagnostic criteria for FAS, because brain dysfunction is not included as a diagnostic feature of FAS in the Hoyme guidelines.

Because of concerns regarding the Hoyme FAS diagnostic criteria, namely, (1) they relax the FAS facial phenotype criteria without confirming the phenotype's specificity for FAS or prenatal alcohol exposure, (2) they allow FAS to be diagnosed when prenatal alcohol exposure is unknown, with the use of FAS facial criteria of unknown specificity for prenatal alcohol exposure, (3) they require confirmation of excessive prenatal alcohol exposure, when documentation of prenatal alcohol exposure is typically unreliable, (4) they include only structural/morphologic measures of CNS damage and exclude functional and neurologic measures of CNS damage, (5) they allow a single structural abnormality to serve as evidence of CNS damage, while relaxing the criterion for one of the key structural features (OFC) into the normal range (≤10th percentile), and (6) the diagnostic guidelines were created by using a nonrepresentative population base (South Africans and Native Americans) and invalid application of a measurement tool (white lip-philtrum guide), this study was conducted to assess the performance of the Hoyme FAS diagnostic criteria when applied to 2 populations, namely, the University of Washington FASD clinical population (a large population that is highly representative of a US population seeking FASD diagnostic services) and a group of high-functioning children with confirmed absence of prenatal alcohol exposure, enrolled as control subjects in a research study. The specific aims of this study were (1)

A

5-point Likert Rank for philtrum and lip	*z* score[a] for palpebral fissure length	Circle the ABC scores for: Palpebral fissure length	Philtrum smoothness	Upper-lip thinness
4 or 5	≤−2 SD	**C**	**C**	**C**
3	>−2 SD and ≤−1 SD	**B**	**B**	**B**
1 or 2	>−1 SD	**A**	**A**	**A**

B

4-digit facial rank	Level of expression of FAS facial features	Palpebral fissure: philtrum-lip ABC-score combinations
4	Severe	CCC
3	Moderate	CCB, CBC, BCC
2	Mild	CCA, CAC, CBB, CBA, CAB, CAA BCB, BCA, BBC, BAC ACC, ACB, ACA, ABC, AAC
1	None	BBB, BBA, BAB, BAA ABB, ABA, AAB, AAA

FIGURE 2
The 4-Digit facial rank[5] (rank of 1–4) is calculated by deriving the facial ABC-Score, which reflects the PFL, philtrum smoothness, and upper lip thinness (A), and converting the facial ABC-Score to the 4-digit rank for face (B). For example, an individual with PFL of −3 SD, philtrum rank 3, and lip rank 1 would receive a facial ABC-Score of CBA and a 4-Digit facial rank of 2. [a]The *z* score reflects how many SDs above or below the mean the patient's PFL is.

to assess the specificity of the Hoyme FAS facial phenotype for the Hoyme FAS diagnosis when the Hoyme guidelines were applied to the University of Washington FASD clinical population, (2) to assess the specificity of the Hoyme FAS facial phenotype to prenatal alcohol exposure when the Hoyme diagnostic guidelines were applied to a study population with confirmed absence of prenatal alcohol exposure, (3) to compare the prevalence of FAS (with and without confirmed prenatal alcohol exposure) between the Hoyme and 4-Digit Code criteria for FAS, when the 2 sets of criteria were applied to the University of Washington FASD clinical population, and (4) to compare, on a case-by-case basis, which patients did and did not receive a diagnosis of FAS when the Hoyme and 4-Digit Code FAS criteria were applied to the University of Washington FASD clinical population.

METHODS

FASD Clinical Population

The target clinical population for this study included all patients diagnosed to date at the University of Washington FAS DPN clinic. A comprehensive set of data (>2000 fields of information, documenting prenatal and lifetime exposures and outcomes, including standardized facial photographs) is collected and entered into a database for each patient who receives a FASD diagnostic evaluation at the FAS DPN clinic, with informed consent and University of Washington Human Subjects Review Board approval. More than 98% of patients provide consent; therefore, the data set is highly representative of the entire University of Washington FAS DPN patient population. All FAS DPN patients have been diagnosed by an interdisciplinary clinical team[10] with the 1997, 1999, or 2004 version of the 4-Digit Diagnostic Code.[2–5] The records of all patients who met the inclusion criteria were included in this study; there were no exclusion criteria. The inclusion criteria were as follows: (1) the patient received an interdisciplinary FASD diagnostic evaluation at the University of Washington FAS DPN clinic with the FASD 4-Digit Diagnostic Code; (2) the patient gave consent for use of the FAS DPN clinical data for research purposes; and (3) all data required to render a FAS diagnosis with the Hoyme guidelines (ie, measures of growth, face, brain growth and/or morphogenesis, and prenatal alcohol exposure) were available in the patient's record.

Research Population With No Alcohol Exposure

The records of 16 children with confirmed absence of prenatal alcohol exposure, who were enrolled as control subjects in a recently completed MRI research study, were also included in this study.[15] The MRI study was

conducted with subject consent and University of Washington Human Subjects Review Board approval. Because only 4 of the 952 patients in the FASD clinical population had a confirmed absence of prenatal alcohol exposure, this larger data set of unexposed subjects was included for better assessment of the specificity of the Hoyme FAS facial phenotype for prenatal alcohol exposure. If the Hoyme FAS facial phenotype is specific to (caused only by) prenatal alcohol exposure, then none of these children should have the FAS facial phenotype. The 16 children in this study population were 8 to 15 years of age; 8 were female, 13 were white, 2 were black, and 1 was Asian American. Their Wechsler Intelligence Scale for Children-III full-scale IQs ranged from 112 to 133.

Hoyme FASD Diagnostic Guidelines

The Hoyme criteria (Table 2) for the diagnostic classifications of FAS with confirmed maternal alcohol exposure and FAS without confirmed maternal alcohol exposure were applied to the 2 study populations. These criteria were used to generate 2 outcome variables, namely, Hoyme FAS facial phenotype (present or absent) and Hoyme FAS diagnosis with or without confirmed maternal alcohol use (present or absent). Because the criteria for these diagnostic outcomes are based solely on physical features measured on numeric scales (eg, height, weight, palpebral fissure length [PFL], and head circumference), computer algorithms were written and applied to the electronic data sets to generate the outcome variables. This eliminated any potential for human error, bias, or interrater discordance.

FASD 4-Digit Diagnostic Code (2004)

All patients in the clinical study population (n = 952) had been diagnosed previously by the University of Washington interdisciplinary FASD diagnostic team. Their 4-Digit Diagnostic Codes and all exposure and outcome data collected for their diagnostic evaluations were recorded in the FAS DPN clinical database. The FASD 4-Digit Diagnostic Code was first printed in 1997 and was updated in 1999 and 2004. For the purposes of this study, all FASD 4-Digit Codes were updated to reflect the 2004 version of the FASD 4-Digit Diagnostic Code.[5] These updates included use of the black lip-philtrum guide and black PFL normative values[16] for all black patients, use of the upper lip circularity tables to rank lip thinness, use of the new growth rank tables, and coding of full-scale IQ of ≤60 as CNS rank 3 rather than rank 4. Because all updates were simply numeric transformations of existing numeric data, the 4-Digit Codes were updated to the 2004 criteria by writing computer transformation algorithms and applying them to the existing data set. Therefore, there was no risk of human error, bias, or interrater discordance in the updating process. All subjects in the MRI study population received a 2004, 4-Digit Diagnostic Code at the time of the MRI study. Therefore, their 4-Digit Codes did not require updating.

The 4 digits of the diagnostic code reflect the magnitude of expression of the 4 key diagnostic features of FASD, in the following order: (1) growth deficiency, (2) FAS facial phenotype, (3) CNS abnormalities, and (4) prenatal alcohol exposure (Figs 1–3). A detailed description of the 4-Digit Code is presented in the *Diagnostic Guide for Fetal Alcohol Syndrome and Related Conditions: The 4-Digit Diagnostic Code*.[5] Briefly, the magnitude of expression of each feature is ranked independently on a 4-point Likert scale, with 1 reflecting complete absence of the FAS feature and 4 reflecting a strong "classic" presence of the FAS feature. Each Likert rank is specifically case defined. There are 256 possible 4-digit diagnostic codes, ranging from 1111 to 4444. Each 4-digit diagnostic code falls into 1 of 22 unique clinical diagnostic categories (labeled A through V). Eight of the 22 diagnostic categories (categories A–C and E–I) fall broadly under the designation of FASD. This study focuses on diagnostic categories A and B, that is, FAS (alcohol exposed) and FAS (alcohol exposure unknown), respectively. The 2004 criteria for these 2 diagnostic categories are presented in Table 3 in a format to facilitate direct comparison with the Hoyme FAS criteria in Table 2. This study also focuses on the FAS facial phenotype. The 4-point ranking system for the 4-Digit Code FAS facial phenotype is presented in Figs 2 and 3. The 4-point ranking system for growth deficiency is as follows: rank 1, height and weight of >10th percentile; rank 2, height or weight of ≤10th percentile but >3rd percentile; rank 3, height or weight of ≤3rd percentile; rank 4, height and weight of ≤3rd percentile. The 4-point ranking system for the CNS is as follows: rank 1, no evidence of dysfunction/delay; rank 2, evidence of

TABLE 2 Hoyme Diagnostic Criteria for FAS With or Without Confirmed Maternal Alcohol Exposure[8]

FAS with confirmed maternal alcohol exposure requires all features A–D
A Evidence of prenatal and/or postnatal growth retardation
1. Height or weight of ≤10th percentile, corrected for racial normative values, if possible
B. Evidence of a characteristic pattern of minor facial anomalies, including ≥2 of the following:
1. Short palpebral fissures (≤10th percentile, equivalent to ≥1.28 SDs below the mean)
2. Thin vermilion border of upper lip (score 4 or 5 on the Lip-Philtrum Guide)
3. Smooth philtrum (score 4 or 5 on the Lip-Philtrum Guide)
C. Evidence of deficient brain growth or abnormal morphogenesis, including ≥1 of the following:
1. Structural brain abnormalities
2. Head circumference of ≤10th percentile
D. Confirmed maternal alcohol exposure; a pattern of excessive intake characterized by substantial regular intake or heavy episodic drinking
FAS without confirmed maternal alcohol exposure requires features A, B, and C

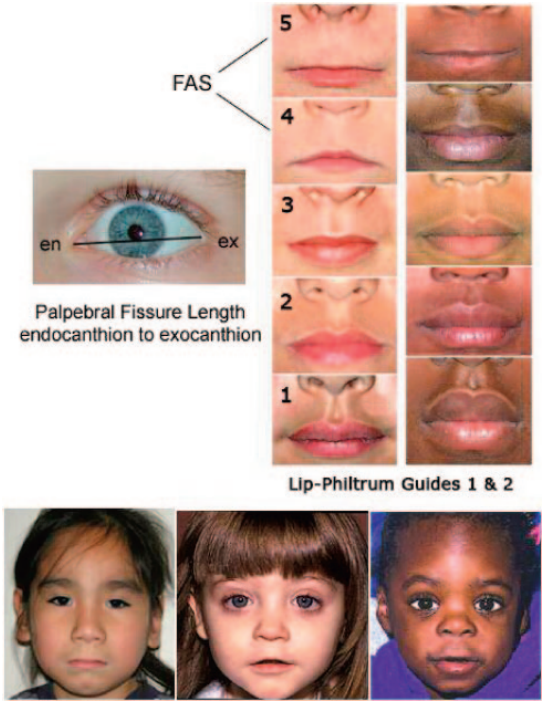


FIGURE 3
Four-Digit Code FAS facial phenotype. The rank 4 FAS facial phenotype determined with the 4-Digit Diagnostic Code[5] requires the presence of the following 3 anomalies: (1) PFL below −2 SD, (2) smooth philtrum (rank 4 or 5 on the Lip-Philtrum Guide), and (3) thin upper lip (rank 4 or 5 on the Lip-Philtrum Guide). Examples of the rank 4 FAS facial phenotype for Native American, white, and black children are shown. The endocanthion and exocanthion are standardized facial landmarks.

moderate dysfunction; rank 3, evidence of severe dysfunction; rank 4, evidence of structural or neurologic damage. The 4-point ranking system for prenatal alcohol exposure is as follows: rank 1, confirmed absence of alcohol exposure from conception to birth; rank 2, alcohol exposure unknown; rank 3, exposure is confirmed and the level of exposure is low-moderate or unknown; rank 4, exposure is confirmed and level is high. More-detailed case definitions of these ranks have been published.[5]

This study did not compare the other diagnoses (partial FAS, alcohol-related neurodevelopmental disorder [ARND], and alcohol-related birth defects [ARBD]) under the designation of FASD across the 2 diagnostic systems, for the following reasons. The Hoyme criteria for partial FAS and ARND include "evidence of a complex pattern of behavioral or cognitive abnormalities," but the Hoyme description of this complex pattern is not specific enough for reliable application of the criteria to the FAS DPN data set. For example, the Hoyme guidelines do not define how severe the abnormalities must be (1 SD below the mean? 2 SDs below the mean?) or how many domains of function must be impaired (2 domains? 3 domains?) to constitute a complex pattern. In contrast, the 4-Digit Code, CDC guidelines, and Canadian guidelines provide specific thresholds (eg, ≥3 domains of function, ≥2 SDs below the mean) (Table 1). The Hoyme criteria for ARBD could not be compared across the 2 systems because, like the CDC guidelines and the Canadian guidelines, the 4-Digit Code does not recognize ARBD as a medical diagnostic classification.

Analysis

The prevalence of FAS in the FASD clinical population was computed by using the 2004, 4-Digit Code and Hoyme criteria for FAS (with and without confirmed prenatal alcohol exposure). The number of patients who met the Hoyme criteria for the FAS facial phenotype was computed for both study populations. The specificity of the Hoyme FAS facial phenotype for the Hoyme FAS diagnosis was computed as follows: number of patients without the Hoyme FAS facial phenotype divided by number of patients without a Hoyme diagnosis of FAS. The specificity of the Hoyme FAS facial phenotype for prenatal alcohol exposure was computed as follows: number of patients without the Hoyme FAS facial phenotype divided by number of patients with a confirmed absence of prenatal alcohol exposure. Each estimate of specificity was accompanied by a 95% confidence interval (CI). Specificity refers to the ability of a test or outcome to indicate nondisease when no disease is present. If an outcome is not specific, then it indicates falsely the presence of disease in nondiseased subjects. A binomial test was used to compare the observed frequency of the Hoyme FAS facial phenotype with the expected frequency (0%) among the 16 children with confirmed absence of prenatal alcohol exposure.

RESULTS

Hoyme Guidelines Applied to the FASD Clinical Population

Study Group

Of the 956 patients diagnosed to date in the FAS DPN Clinic, 952 (99.6%) met the inclusion criteria for this study (Table 4). Therefore, this study population is highly representative of the entire FAS DPN patient population seen over 13 years. The study population represents a racially diverse group, ranging in age from 0.2 and 50.8 years of age at the time of the FASD diagnostic evaluation. A total of 732 of the patients (77%) had 2004, 4-Digit Codes that fell under the general designation of FASD. An additional 147 (15%) had growth, facial, and/or CNS abnormalities but their prenatal alcohol exposures were unknown. An additional 4 patients had a confirmed absence of prenatal alcohol exposure. Therefore, this patient population reflects the range of outcomes and exposures encountered typically by a FASD diagnostic clinic; not all patients referred to

TABLE 3 **Four-Digit Code Diagnostic Criteria for FAS With and Without Confirmed Prenatal Alcohol Exposure[5]**

FAS with confirmed prenatal alcohol exposure requires all features A–D[a]
- A. Evidence of prenatal and/or postnatal growth retardation (growth rank 2, 3, or 4); height and/or weight of ≤10th percentile, corrected for race and midparental height when possible
- B. Presence of all 3 of the following minor facial anomalies (facial rank 4):
  1. Short palpebral fissures (≥2 SDs below the mean, equivalent to ≤2.5th percentile)
  2. Thin upper lip (rank 4 or 5 on Lip-Philtrum Guide 1 or 2, as appropriate for race)
  3. Smooth philtrum (rank 4 or 5 on Lip-Philtrum Guide 1 or 2, as appropriate for race)
- C. Evidence of ≥1 of the following (CNS rank 3 or 4):
  1. Structural brain abnormalities
     a. Structural brain abnormalities (as may be viewed by brain imaging)
     b. Microcephaly (head circumference ≥2 SDs below the mean, equivalent to ≤2.5th percentile)
  2. Neurologic abnormalities
     a. Seizure disorder of prenatal origin
     b. Hard neurologic signs (eg, cerebral palsy)
  3. Significant brain dysfunction
     a. Three or more domains of brain function, ≥2 SDs below the mean, when assessed with validated, standardized, psychometric tools; domains may include but are not limited to executive function, memory, cognition, and language
- D. Confirmed prenatal alcohol exposure (alcohol rank 3 or 4); a specific pattern or level of exposure is not required because it is rarely known when this information has been obtained reliably in a clinical setting and the risk of a specific pattern of exposure is not identical across all fetuses

FAS without confirmed prenatal alcohol exposure requires features A, B, and C, with prenatal alcohol exposure not confirmed to be present and not confirmed to be absent[b]

[a] These criteria reflect the following 2004, 4-Digit Diagnostic Codes: 2433, 2434, 2443, 2444, 3433, 3434, 3443, 3444, 4433, 4434, 4443, and 4444.
[b] These criteria reflect the following 2004, 4-Digit Diagnostic Codes: 2432, 2442, 3432, 3442, 4432, and 4442.

the clinic receive a diagnosis under the designation of FASD.

Specific Aim 1

Thirty-five percent of the patients (330 of 952 patients) met the Hoyme criteria for the full FAS facial phenotype. Only 39 (11.8%) of the 330 patients with the Hoyme FAS facial phenotype met the Hoyme criteria for a diagnosis of FAS (with or without confirmed maternal alcohol use). The specificity of the Hoyme FAS facial phenotype for the Hoyme FAS diagnosis in this clinical population was 68% (622 of 913 patients; 95% CI: 65%–71%). Of the 330 patients with the Hoyme FAS facial phenotype, most did not present with other features of FAS; 60% presented with no growth deficiency (height and weight percentiles of >10th percentile), 74% did not have the 4-digit FAS facial phenotype (rank 4), 82% did not have microcephaly (OFC of ≤2.5th percentile), 77% had an OFC of >10th percentile; 89% of the 32 clinically indicated MRI studies were normal; and 64% of subjects did not have confirmed, excessive, prenatal alcohol exposure. It is worth noting that an additional 84 (25%) of the 330 patients would likely meet the Hoyme criteria for partial FAS (with or without confirmed maternal alcohol use). This is based on the assumption that the Hoyme criteria for a complex pattern of behavioral or cognitive abnormalities are comparable to the 4-digit CNS rank 3. However, 24 of these 84 children had no evidence of brain damage/dysfunction. Their only impairment was growth deficiency. If the specificity of the Hoyme FAS facial phenotype is computed for the Hoyme diagnoses of FAS plus partial FAS, then specificity increases, but only to 75% (622 of 829 subjects; 95% CI: 72%–78%).

Specific Aim 3

The prevalence of FAS (with or without confirmed prenatal alcohol exposure) determined with the 2004, 4-Digit Code was 3.7% (35 of 952 subjects). The prevalence of FAS (with or without confirmed maternal alcohol use) determined with the Hoyme FASD guidelines was 4.1% (39 of 952 subjects). Although the prevalences were similar, the patients identified with the 2 systems were not. Only 17 patients met both the 4-Digit Code and Hoyme criteria for FAS.

Specific Aim 4

Of the 39 patients who met the Hoyme criteria for FAS, 22 (56.4%) did not meet the 4-Digit Code criteria for FAS. The 22 patients ranged in age from 0.8 to 21.4 years and were racially diverse (white, 64%; black, 14%; Native American, 0%; other, 22%). They did not meet the 4-Digit Code criteria for FAS for ≥1 of the following reasons. Thirteen (59%) had facial phenotypes within the normal range (facial rank 2), as defined with the 4-Digit Code. Two had unknown prenatal alcohol exposures and facial features that were too mild (rank 2 or 3, not sufficiently specific for FAS) to allow labeling of the outcome as FAS in the absence of confirmed exposure. Seven (32%) met the 4-Digit Code for Partial FAS.

To portray just how different the Hoyme and 4-Digit Code criteria for FAS are, the outcomes for 1 of the 22

TABLE 4 **Sociodemographic and Clinical Profile of University of Washington FAS DPN Clinical Study Population**

Characteristic	Total Sample ($N = 952$)
Female gender, *n* (%)	416 (43.8)
Race, *n* (%)	
White	490 (51.5)
Black	53 (5.6)
Native American	59 (6.2)
Hispanic (full or mixed race)	107 (11.2)
Asian (full or mixed race)	15 (1.6)
Other (full or mixed race)	228 (23.9)
Age at time of diagnosis, y	
Mean ± SD	10.2 ± 7.4
Range	0.2–50.8
Age distribution, *n* (%)	
0–2.9 y	101 (10.6)
3–10 y	452 (47.9)
11–17 y	295 (31.0)
≥18 y	100 (10.5)
2004, 4-Digit Diagnostic Categories, *n* (%)	
A (FAS; alcohol exposed)[a]	29 (3.0)
B (FAS; alcohol exposure unknown)[a]	6 (0.6)
C (partial FAS; alcohol exposed)[a]	46 (4.8)
E (physical findings/static encephalopathy; alcohol exposed)[a]	58 (6.1)
F (static encephalopathy; alcohol exposed)[a]	163 (17.1)
G (physical findings/neurobehavioral disorder; alcohol exposed)[a]	87 (9.1)
H (neurobehavioral disorder; alcohol exposed)[a]	323 (33.9)
I (physical findings; alcohol exposed)	20 (2.1)
J (no physical findings or CNS abnormalities detected; alcohol exposed)	58 (6.1)
K (physical features/static encephalopathy; alcohol exposure unknown)	16 (1.7)
L (static encephalopathy; alcohol exposure unknown)	39 (4.1)
M (physical findings/neurobehavioral disorder; alcohol exposure unknown)	26 (2.7)
N (neurobehavioral disorder; alcohol exposure unknown)	66 (6.9)
P (no physical findings or CNS abnormalities detected; alcohol exposure unknown)	11 (1.2)
Q (physical findings/static encephalopathy; confirmed absence of exposure)	1 (0.1)
R (static encephalopathy; confirmed absence of exposure)	1 (0.1)
S (physical findings/neurobehavioral disorder; confirmed absence of exposure)	1 (0.1)
T (neurobehavioral disorder; confirmed absence of exposure)	1 (0.1)

[a] These categories fit under the designation FASD.

children (a 14-year-old white youth) who met the Hoyme criteria for FAS but not the 4-Digit criteria for FAS are presented in Fig 4. The 4-Digit Code did not classify this child as having FAS or any diagnosis under the designation of FASD, because alcohol exposure was unknown and the outcomes observed in this child (short stature and microcephaly) were not specific to FAS. Because the Hoyme guidelines require that only 2 of the 3 FAS facial features be present (in this case, PFL in the 1st percentile and philtrum rank 4), this child can and does present with a very thick upper lip (Lip-Philtrum Guide rank 1). This results in a facial phenotype that neither looks dysmorphic nor resembles FAS (Fig 4). The facial features of this child were measured at the time of diagnosis, directly by 2 clinicians and through photographic analysis, with concordance across all 3 measurements. Photographic examples of the rank 4 FAS facial phenotype, as defined with the 4-Digit Code, are presented for comparison in Fig 3.

Conversely, of the 35 patients who met the 4-Digit Code criteria for FAS, 18 (51.4%) did not meet the Hoyme criteria for FAS. The 18 patients ranged in age from 1.5 to 24.3 years and were racially diverse (white, 39%; black, 11%; Native American, 0%; other, 50%). They did not meet the Hoyme criteria for FAS for ≥1 of the following reasons. Seven (39%) did not have evidence of structural brain anomalies, but all 7 had evidence of significant brain dysfunction (4-Digit Code CNS rank 3) (Table 1), including 3 with IQ scores between 56 and 64. Twelve (67%) had confirmed prenatal alcohol exposure (4-Digit Code alcohol rank 3), but information was not available to confirm that exposure was excessive (4-Digit Code alcohol rank 4). Six of these 12 children had 4-digit codes of 4443, which demonstrates clearly that confirmed excessive exposure is not required for a child to present with the most severe end of the spectrum for growth deficiency, FAS facial features, and CNS damage. Six children (33%) likely would have met the Hoyme criteria for partial FAS. These individuals had significant brain dysfunction (4-Digit CNS rank 3) but no known evidence of structural brain anomalies.

Hoyme Guidelines Applied to the Population With Confirmed Absence of Prenatal Alcohol Exposure

Specific Aims 2 and 3

When the Hoyme criteria for the FAS facial phenotype were applied to the 16 children with confirmed absence of prenatal alcohol exposure who were enrolled as control subjects in a MRI research study, 4 (25%) of the 16 children met the Hoyme criteria for the FAS facial phenotype. This observed frequency of 25% was significantly greater than the expected frequency of 0% (binomial test, $P < .001$). The specificity of the Hoyme FAS facial phenotype for prenatal alcohol exposure in this study population was 75% (12 of 16 children; 95% CI: 50%–89%). All 4 subjects had normal growth, normal facial phenotypes according to the 4-Digit Code (facial rank 2), normal OFCs, normal cranial MRI results, and neuropsychological performance significantly above average, including full-scale IQ scores between 124 and 128. None of the 16 children met the 4-Digit Code criteria for the FAS facial phenotype (rank 4). The sole purpose of including these 16 children in this study was to assess the specificity of the FAS facial phenotype for prenatal alcohol exposure. For the sake of completeness,

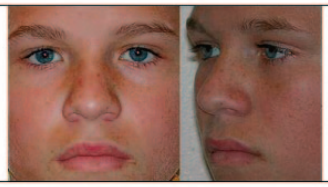
Features		4-Digit Code
Growth	[a]Height 1st percentile (parental heights unknown) Weight 12th percentile	Rank 3
Face	[a]PFL: 1st percentile (-2.9 SD) [a]Philtrum: somewhat smooth: rank 4 Lip: thick: rank 1 No other facial anomalies present 	Rank 2
CNS	[a]OFC 1st percentile (-2.2 SD) Brain function in the low-normal range, including an FSIQ = 95	Rank 4 Rank 2
Alcohol	[a]Unknown	Rank 2
4-digit code diagnosis	Sentinel physical findings/static encephalopathy/alcohol exposure unknown	3242
Hoyme diagnosis	FAS (unknown maternal alcohol exposure)	

FIGURE 4
Example of a 14-year-old child who met the Hoyme FAS criteria but not the 4-Digit Code FAS criteria. [a]Features that allowed the child to meet the Hoyme criteria for FAS (maternal alcohol exposure unknown). FSIQ indicates full-scale IQ.

it could be stated that none of the 16 children met the Hoyme or 4-Digit criteria for a diagnosis of FAS, but this was known from the start. By definition, an individual who was not exposed to alcohol cannot be at risk for FAS.

It is interesting to note that, although only 4 of the 952 patients in the FASD clinical population had a confirmed absence of prenatal alcohol exposure, 1 (25%) of those 4 also met the Hoyme criteria for the full FAS facial phenotype. The child had a normal facial phenotype according to the 4-Digit Code (rank 2) and was growth deficient (rank 4). This observation also reflects a specificity of 75%.

DISCUSSION

Specificity of the FAS Facial Phenotype and Its Impact on Diagnosis

This study demonstrated that an extraordinary number of patients in the FAS DPN clinic met the Hoyme criteria for the full FAS facial phenotype (35%; 330 of 952 subjects), whereas very few of them met the Hoyme criteria for a diagnosis of FAS (11.8%; 39 of 330 subjects). If the Hoyme FAS facial phenotype were specific to FAS, then it would be expected that the vast majority of those with the FAS face would have FAS; the opposite was observed, however. The vast majority of those with the FAS face (88.2%; 291 of 330 subjects) did not have FAS. If the Hoyme FAS face were specific to (caused only by) prenatal alcohol exposure, then individuals could not have the FAS face if they had not been exposed to alcohol. However, this study found that 25% of the children with confirmed absence of prenatal alcohol exposure, in both study populations, met the criteria for the Hoyme FAS face.

Although these results are concerning, they were not unexpected. By relaxing 1 of the facial criteria into the normal range (PFL of ≤10th percentile), requiring only 2 of 3 features to be present, and allowing the 2 features to be expressed at the mildest end of the spectrum (for example, a white subject with a PFL in the 10th percentile with a somewhat smooth philtrum [rank 4] but a very thick upper lip [rank 1]), the diagnostic criteria identify many individuals with normal facial phenotypes. One hundred fifty of the 330 patients with the Hoyme FAS facial phenotype had facial phenotypes that were only rank 2 according to the 4-Digit Code. Rank 2 (by definition) is well within the normal range for the general population.

Although the primary focus of this study was on the diagnosis of FAS, the relaxed Hoyme FAS facial criteria also jeopardize the clinical validity of the Hoyme criteria for partial FAS. The Hoyme criteria for partial FAS use the same relaxed criteria for the FAS facial phenotype and require only 1 other feature to be present (growth deficiency, deficient brain growth or abnormal morphogenesis, or evidence of a complex pattern of behavioral or cognitive abnormalities). Confirmed prenatal alcohol exposure is not required. Therefore, a white individual who presents with the following features would meet the Hoyme criteria for partial FAS: growth, height in the 10th percentile and weight in the 95th percentile; face, PFL in the 10th percentile, somewhat smooth philtrum (rank 4), and very thick upper lip (rank 1); CNS, normal structure and function; alcohol, unknown exposure. With the 4-Digit Code, this child would not even fall under the designation of FASD, because the outcomes are in the normal to very mildly impaired range, the only impaired outcome (height in the 10th percentile) is not specific for prenatal alcohol exposure, and alcohol exposure is unknown. In contrast to the Hoyme guidelines, the 4-Digit Code requires confirmed prenatal alcohol exposure for partial FAS, because the 4-Digit diag-

nosis of Partial FAS allows the facial criteria to be relaxed to facial rank 3 in some instances. Facial rank 3 is less specific for FAS and prenatal alcohol exposure; therefore, the 4-Digit Code does not allow it to be used as a proxy measure of prenatal alcohol exposure for partial FAS when prenatal alcohol exposure is unknown.

Why are the sensitivity and specificity of the FAS facial phenotype so important for the medical validity of a diagnosis of FAS? When we make a diagnosis of FAS, we are stating implicitly that the individual has a syndrome caused by prenatal alcohol exposure. We are also stating implicitly that the birth mother drank alcohol during pregnancy and, as a result, harmed her child. These are bold conclusions to draw and are not without medical and ethical consequences. How confident are we when we infer a causal link between an individual's prenatal alcohol exposure and his or her syndromic features, especially when 2 of the 3 diagnostic features of this syndrome (growth deficiency and CNS damage/dysfunction) are not specific to (caused only by) prenatal alcohol exposure. The validity of the diagnosis rests solely on the specificity of the facial phenotype for the exposure (alcohol) and the outcome (FAS). If a cluster of facial features truly is unique to prenatal alcohol exposure (meaning that alcohol is the only agent that can cause this facial phenotype) and is unique to the diagnosis of FAS (meaning that this exact phenotype is not present in any other medical condition), then we would expect to observe the following: (1) the face would be highly sensitive for FAS (individuals with FAS would have the FAS facial phenotype), (2) the face would be highly specific for FAS (individuals without FAS would not have the FAS facial phenotype), and (3) the face would be highly specific for prenatal alcohol exposure (individuals without prenatal alcohol exposure would not have the FAS facial phenotype). The rank 4 FAS facial phenotype, as defined with the 4-digit code, demonstrates all 3 of these qualities.[4,11–14] A highly specific FAS facial phenotype validates the FAS diagnosis, because the presence of the face confirms that individuals were affected by their prenatal alcohol exposure. The face not only confirms that individuals were affected by prenatal alcohol exposure but also confirms that they were exposed to alcohol. We depend on the latter when we render a diagnosis of FAS in the absence of confirmed prenatal alcohol exposure. If the face is truly specific to alcohol, then individuals cannot have the face if they were not exposed to alcohol. This is why all diagnostic guidelines can and do allow FAS to be diagnosed even when prenatal alcohol exposure is unknown. The face is so specific for alcohol exposure that it serves as a valid proxy measure for exposure. This is also why all diagnostic guidelines cannot and do not allow ARND (or its equivalent) to be diagnosed when alcohol exposure is unknown. Because the FAS facial phenotype is not present in ARND, it cannot serve as a proxy measure for alcohol exposure. In the absence of a highly specific facial phenotype, the validity of the diagnostic process breaks down precipitously; individuals' outcomes cannot be linked to their prenatal alcohol exposure, FAS becomes indistinguishable from ARND/fetal alcohol effects, and diagnoses cannot be made when alcohol exposure is unknown. Considering the fundamental role that the FAS facial phenotype plays in FAS diagnosis, its specificity cannot be assumed and must be confirmed through properly designed empirical studies.

The Evidence Base Underlying the FAS Facial Phenotype

A series of empirical laboratory,[17] clinical,[4,12,13] and population-based screening and surveillance[11,14] studies were conducted by Astley, Clarren, and colleagues over the course of 10 years, to establish the evidence base that supports the diagnostic validity of the 4-Digit Code rank 4 FAS facial phenotype. In 2004, the CDC incorporated the 3 facial anomalies into their FAS guidelines but relaxed the PFL criterion from ≤2.5th percentile to ≤10th percentile. The CDC did not report measures of sensitivity or specificity to validate their relaxed facial criteria. The CDC guidelines[6] cite a series of studies that are intended to support their FAS facial phenotype criteria, but relaxation of the PFL criterion actually goes against the evidence-based literature. For example, the CDC guidelines report, "Use of these three cardinal features (smooth philtrum, thin vermilion, and small palpebral fissures) to assess whether an individual's dysmorphia is consistent with FAS is compatible with the IOM report and other diagnostic systems currently in use."[6] The 3 features are "compatible" with the IOM and 4-Digit Code guidelines, but the magnitude of expression of the PFL is not. The IOM guidelines state, "In this area, the palpebral fissures (eye slits) are short, usually measuring well below −2 SD (standard deviation) for age."[1] The mean PFL among all patients diagnosed as having FAS in the Washington State FAS DPN clinic was −4.0 SD (±1.3 SD).[13] Both the IOM and FAS DPN PFL references are substantially below the 10th percentile (or its equivalent, −1.28 SD) criterion set by the CDC. The CDC does report that use of the 3rd percentile cutoff value for the PFL reduces potential false-positive results for the diagnosis. The CDC guidelines also reported that, "Using anthropometric measurements of all facial features, clinical researchers have confirmed the midline feature abnormalities.[18]"[6] In actuality, the study by Moore et al[18] did not include all facial features. Two of the 3 key midline facial features (philtrum smoothness and lip thinness) were never assessed, and the mean PFL among the 41 alcohol-exposed subjects was −3.6 SD (±1.6 SD), again well below the 10th percentile set by the CDC. Finally, the CDC guidelines reported, "Studies of clinic-referred samples also support these features as discriminant for FAS.[13,19]"[6] But Astley and Clarren[13] did not report that these features are discriminant for FAS

when the PFL is relaxed to the 10th percentile. Coles et al[19] did not include a study group diagnosed as having FAS, did not report what facial features were assessed, and did not conduct a discriminant analysis to delineate the FAS facial phenotype.

In 2005, the Hoyme criteria[8] further relaxed the diagnostic criteria for the FAS facial phenotype to ≥2 of the 3 CDC facial criteria. Like the CDC, Hoyme et al[8] did not provide measures of sensitivity or specificity to validate their relaxed criteria. They also did not report what methods they used (eg, discriminant analyses) to conclude that the facial criteria should be relaxed to 2 features. It is interesting to note that these relaxed criteria are no longer consistent with the facial criteria defined by David Smith, who originally coined the term FAS. In 1979, Smith[20] reported,

> As far as the diagnosis is concerned, perhaps the most important point to emerge in the last few years is that the facial abnormalities seen in affected infants are the key cluster of features that tend to make FAS a clinically discernible entity. Many disorders result in mental and growth deficiency, but in FAS the deficiencies are typically present in a patient whose face has short palpebral fissures, a hypoplastic upper lip with a thinned vermilion border, and a smoothed or absent philtrum. Up to now, the descriptions of the facial features of FAS that have appeared in the literature have not always emphasized the same abnormalities. This has led to some confusion, but inspection of the photographs accompanying these reports leaves no doubt about the facial similarities of FAS patients.

Strengths and Limitations That Affect Validity

The study design and methods used by Hoyme et al[8] to formulate their diagnostic guidelines present both strengths and limitations. Key strengths include the use of skilled multidisciplinary teams led by experts in the field of FASD diagnosis; use of standardized objective measurement tools to enhance reliability; and access to a reasonably large, population-based, study sample. Several limitations, however, jeopardize the validity of the guidelines. (1) Hoyme et al[8] reported that the objective of their study was to formulate more-precise clarifications of the 1996 IOM diagnostic guidelines[1] for "general pediatric practice." However, the racial distribution of their study population (92 South Africans[21] and 72 Native Americans[22]) is not representative of their intended target population (general pediatric practice). (2) Hoyme et al[8] used data for previously diagnosed South African and Native American patients (1998–2003)[22] to formulate their diagnostic criteria. However, an incorrect lip-philtrum guide (white) was used to measure lip thinness in their South African population. Use of a white Lip-Philtrum Guide for a predominantly South African population would result in substantial diagnostic misclassification. The direction of error would be to underestimate the prevalence of the FAS facial phenotype. Creation of diagnostic criteria from a data set predominated by subjects who had a key facial feature measured with an incorrect tool would jeopardize the clinical validity of those criteria. Hoyme et al[8] reported, "A weakness of the proposed diagnostic approach is that the normative values currently used for growth and facial morphologic features are based largely on white populations." The black Lip-Philtrum Guide was made available to clinicians in 2003, before the publication of the Hoyme diagnostic guidelines in 2005. Because the black Lip-Philtrum Guide was not available at the time the South African population was being diagnosed, the South African population may not have been an appropriate population to include in the formulation of the Hoyme guidelines. (3) The Hoyme guidelines described the Lip-Philtrum Guide as follows: "A score of 1 is considered completely normal, whereas a score of 5 is most indicative of FAS."[8] This is incorrect; a score of 1 is highly abnormal. The Lip-Philtrum Guide reflects a normal curve in which rank 3 is the mean (50th percentile) and ranks 1 and 5 reflect the extreme ends of the normal curve (<2.5th percentile and >97.5th percentile, respectively). Rank 4 for the lips and philtrum is not 4 ranks above normal but only 1 rank above normal. Therefore, relaxation of the facial criteria to just 2 of the 3 features, while allowing the 2 features to be expressed near or within the normal range (rank 4 or 10th percentile), would identify a preponderance of individuals with normal facial phenotypes. This is exactly what occurred when the Hoyme FAS facial criteria were applied to the FAS DPN clinical population and a control population of children with confirmed absence of prenatal alcohol exposure. (4) Finally, Hoyme et al[8] reported, "Our aim was to improve both the reliability and validity of diagnoses within the FASD continuum." They concluded, "Application of our guidelines to our extensive database of children prenatally exposed to alcohol demonstrated that the method was rigorous and accurate."[8] The authors convey an important point, that is, guidelines should undergo rigorous evaluation of their performance. However, the authors did not report standardized measures of reliability (eg, test-retest and interrater reliability), validity (eg, construct validity, convergent validity, and criterion validity), or accuracy (eg, sensitivity, specificity, and positive and negative predictive values). These measures have been assessed, confirmed to be high, and published for the 4-Digit Code.[4,11–14]

Hoyme et al[8] used data for 164 children to formulate their FASD diagnostic guidelines. These children were diagnosed originally by May and colleagues[21,22] between 1998 and 2003, with a gestalt approach to diagnosis. Hoyme et al[8] reported that 97 of the 164 children received an original gestalt diagnosis of FAS. When Hoyme et al[8] applied their 2005 guidelines to the 164 children, only 59 of the 97 children retained their diagnosis of FAS. Ten of the 59 children did not have confirmed

prenatal alcohol exposures. The remaining 38 received revised diagnoses across the entire spectrum of FASD, documenting the magnitude and prevalence of errors in the original FAS diagnoses. Sixteen of those who were diagnosed originally as having FAS were reclassified as having ARND (ie, reclassified from the full FAS facial phenotype to a complete absence of the FAS facial phenotype). The inaccurate and highly variable diagnostic outcomes that result from the gestalt approach to diagnosis were demonstrated in 2000 by Astley and Clarren.[4] When the 1997 version of the 4-Digit Code was applied to 69 patients who had received previously a gestalt diagnosis of FAS at the University of Washington FAS DPN clinic, only 9 maintained their FAS diagnosis. Sixty lost their diagnosis of FAS because 37 had no evidence of growth deficiency, 27 had only 1 of the 3 FAS facial features, 29 had no psychometric or structural evidence of brain damage, and 5 had unknown exposure to alcohol. The extraordinarily high FAS prevalence rates (40.5–46.4 cases per 1000 subjects) reported by May et al[21] for a South African community were based on FAS diagnoses that Hoyme et al[8] reported were inaccurate and overestimated.

The Potential to Overdiagnose Alcohol-Related Disabilities

Another marked contrast between the 4-Digit Code and the Hoyme guidelines is in the use of the terms ARND and ARBD. The Hoyme guidelines use the terms, and the 4-Digit Code does not. Both sets of guidelines acknowledge that growth deficiency and CNS damage/dysfunction are not specific to prenatal alcohol exposure, a fact that has been accepted in the field of FASD from the start.[20] With regard to the diagnosis of individuals who present with prenatal alcohol exposure and CNS damage/dysfunction but no FAS facial phenotype, Hoyme et al[8] expressed the following concern about the 4-Digit Code.

> The Washington criteria place much emphasis on the encephalopathy and neurobehavioral disorder present among affected children. These 2 findings are not specifically defined and, as general terms, they are not unique to the prenatal effects of alcohol on fetal development. In addition, the family and genetic background of the child is not adequately integrated into the criteria. Because this highly structured system seems all-encompassing, there is the potential for over-diagnosis of alcohol-related disabilities; any child with a disability who has been exposed to alcohol prenatally can be assigned a diagnostic classification easily, even if the cause of the disability is genetic.

To the contrary, the 4-Digit Code cannot overdiagnose alcohol-related disabilities because the 4-Digit Code does not render "alcohol-related" diagnoses. The only diagnoses that the 4-Digit Code links causally (or relates) to prenatal alcohol exposure are FAS and Partial FAS. This is the most important feature of the 4-Digit Code that distinguishes it from all other FASD diagnostic guidelines. The 4-Digit Code was developed with the premise that a diagnosis should be based on verifiable facts, not supposition. The diagnostic nomenclature used by the 4-Digit Code reflects this. Growth deficiency and CNS damage/dysfunction are not specific to (caused only by) prenatal alcohol exposure. When an individual presents in a clinic with prenatal alcohol exposure and CNS damage/dysfunction but does not have the FAS facial phenotype, the damage/dysfunction may be entirely attributable to the prenatal alcohol exposure, partially attributable to the prenatal alcohol exposure, or unrelated to the prenatal alcohol exposure. Current medical technology is unable to confirm or to exclude the etiologic role of alcohol for an individual patient. This does not pose a problem, however. An accurate diagnosis and effective intervention can proceed without confirmation of an etiologic role of alcohol. When an individual presents with CNS damage/dysfunction and prenatal alcohol exposure, the 4-Digit Code names it exactly what it is, that is, static encephalopathy/alcohol exposed if the CNS damage/dysfunction is severe or neurobehavioral disorder/alcohol exposed if the CSN dysfunction is less severe. The terms do not state or imply a causal association between the exposure and outcomes. Rather, including the phrase "alcohol exposed" in the diagnostic terms serves to alert clinical providers that the individual was exposed to a teratogen and thus is at risk for underlying brain damage. Knowledge of this risk is important, because the presence of underlying brain damage could affect the clinician's future care and intervention efforts for that patient. In contrast to the 4-Digit Code, when an individual presents with CNS damage/dysfunction and prenatal alcohol exposure but no FAS facial phenotype, the Hoyme FASD guidelines label the condition alcohol-related neurobehavioral disorder, stating that the patient's neurobehavioral disorder is related to their alcohol exposure. Aase et al[23] argued effectively that clinical use of the term fetal alcohol effects, with its implications of causation, should be abandoned. Those same arguments apply to ARND and ARBD. Clinicians new to the field of FASD diagnosis are encouraged to read that seminal article. Aase et al[23] urged "simple recording of the verifiable conclusions. . . . If prenatal alcohol exposure has taken place, but FAS cannot be substantiated, the exposure still should be indicated, and any nonspecific abnormalities or problems noted." This is exactly what the 4-digit code does. To convey more completely this important and unique feature of the 4-Digit Code, the guidelines provide clinical summary templates for static encephalopathy/alcohol exposed and neurobehavioral disorder/alcohol exposed, which include the following statement: "The diagnosis of static encephalopathy (or neurobehavioral disorder) does not mean that alcohol is the cause of the problem. A number of other factors could be contributing to the present issues, such as the patient's genetic background, other potential ex-

posures or problems during pregnancy, and various experiences since birth."[3,5] The 4-Digit Code devotes an entire chapter and 4-Digit ranking system to documentation of other prenatal (including genetic) and postnatal exposures and events that occur frequently with prenatal alcohol exposure and likely contribute to the outcomes observed for individuals.[3,5] In fact, the vast majority of the 952 patients seen in the University of Washington FAS DPN clinic presented with multiple risk factors (81% were exposed to illicit drugs in utero, 25% had poor prenatal care, 29% had other complications during pregnancy, 2% had other syndromes, 25% were physically or sexually abused, and 70% were in foster/adoptive care). The impact of prenatal alcohol exposure is never assessed in isolation from other risk factors. The Hoyme guidelines state, "FASD must always be a diagnosis of exclusion. Many genetic and malformation syndromes have some of the other clinical characteristics of FAS. If there is no indication of another genetic or malformation syndrome, then the revised IOM criteria can be applied to categorize a diagnosis within the FASD continuum."[8] Overlap between individual symptoms/anomalies is common throughout medicine. An astute clinician would not mistake FAS for William's syndrome simply because the 2 have some but not all features in common, because it is the constellation of features that distinguish the 2 syndromes. The statement that FASD diagnostic criteria should be applied only if there is no indication of another genetic syndrome implies that alcohol is not a teratogen to a child born with another syndrome. Clearly this is not true. A FASD diagnostic team should consider alternative or co-occurring syndromic diagnoses and medical conditions at all times.

CONCLUSIONS

Accurate, reliable, medical diagnoses across the full continuum of FASD have been available to families and clinicians for almost a decade. As medical technology and our understanding of FASD advance, so must our diagnostic methods and tools. It is imperative that advancements in diagnostic methods be guided by an evidence base of rigorously designed, implemented, and peer-reviewed research. When a diagnosis under the designation of FASD is made, 2 individuals are affected directly, namely, the child and the birth mother. The consequences of an incorrect diagnosis for both mother and child must be considered carefully. Diagnostic guidelines should guide professionals in rendering an accurate medical diagnosis. A diagnosis reflects the condition of a patient; however, because a diagnosis serves many purposes (eg, treatment, prevention, communication among specialists, and qualification for services), the process of rendering a diagnosis can sometimes be influenced by those different purposes. The only diagnosis that serves all purposes most effectively is a correct diagnosis. Access to services should be based on an individual's disabilities and not on what caused their disabilities. Therefore, services should be available for individuals across the full continuum of FASD and not just those with FAS.

It is critical to identify all individuals at risk for FASD. This is achieved through screening and not through relaxation of diagnostic criteria. Screening criteria typically use relaxed diagnostic criteria to identify correctly all individuals with the disease (true-positive results). However, this comes at the risk of incorrectly identifying some individuals who do not have the disease (false-positive results). All subjects identified as screen-positive receive a comprehensive diagnostic evaluation. It is at that time that accurate diagnoses are rendered and the false-positive screens are confirmed to be false-positive results. Through this process, an individual may receive a false-positive screening outcome. No one should receive a false-positive diagnosis, however.

Patients and their families deserve accurate diagnoses. Effective intervention and prevention require accurate diagnoses. Professionals now have access to several FASD diagnostic guidelines. Ultimately they will decide which guidelines are adopted into practice. Their decision will be influenced in large part by a measure of validity that is not easily quantified, namely, construct validity, the extent to which the guidelines produce meaningful results that are commensurate with their clinical impression.

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Exploring the Utility of Narrative Analysis in Diagnostic Decision Making: Picture-Bound Reference, Elaboration, and Fetal Alcohol Spectrum Disorders

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Purpose: To evaluate classification accuracy and clinical feasibility of a narrative analysis tool for identifying children with a fetal alcohol spectrum disorder (FASD).
Method: Picture-elicited narratives generated by 16 age-matched pairs of school-aged children (FASD vs. typical development [TD]) were coded for semantic elaboration and reference strategy by judges who were unaware of age, gender, and group membership of the participants. Receiver operating characteristic (ROC) curves were used to examine the classification accuracy of the resulting set of narrative measures for making 2 classifications: (a) for the 16 children diagnosed with FASD, low performance ($n = 7$) versus average performance ($n = 9$) on a standardized expressive language task and (b) FASD ($n = 16$) versus TD ($n = 16$).
Results: Combining the rates of semantic elaboration and pragmatically inappropriate reference perfectly matched a classification based on performance on the standardized language task. More importantly, the rate of ambiguous nominal reference was highly accurate in classifying children with an FASD regardless of their performance on the standardized language task (area under the ROC curve = .863, confidence interval = .736–.991).
Conclusion: Results support further study of the diagnostic utility of narrative analysis using discourse level measures of elaboration and children's strategic use of reference.

KEY WORDS: assessment procedures, pragmatics, discourse analysis, language sample analysis, diagnostics

Narrative discourse permeates our social lives from an early age, making it a critical area to address in the measurement of language abilities. For more than 2 decades, narrative analysis has been recommended as an ecologically valid way to assess the production of meaningful language in socially integrated discourse (see Owens, 1999). Underlying this recommendation is the assumption that narrative analysis provides a more integrated appraisal of a child's communicative abilities than is possible via standardized language measures (Adams, Lloyd, Aldred, & Baxendale, 2006; Botting & Adams, 2005; Culatta, Page, & Ellis, 1983; Norbury & Bishop, 2003; Wagner, Nettelbladt, Sahlen, & Nilholm, 2000). Thus, narrative analysis should be able to identify children with meaningful communicative impairments that might be missed using conventional standardized assessment instruments. The current study examined this largely untested assumption by retrospectively comparing narratives produced by school-aged children with a fetal alcohol spectrum disorder (FASD) with those produced by age- and gender-matched

typically developing (TD) peers. Comparisons were made via the Semantic Elaboration Coding System[1] (Thorne, 2004), which systematically measures the use of pragmatically appropriate strategies of reference and the semantic elaboration of concepts.

FASDs and Language

Children with prenatal alcohol exposure exhibit a wide range of abilities across all body systems (Astley & Clarren, 2000; Carmichael-Olson, Morse, & Huffine, 1998; Streissguth, 1997). When specific growth, facial, and central nervous system impairments are present within a well-specified range, a diagnosis from within the continuum of FASD can be rendered (see Astley, 2004; Chudley et al., 2005). Because the development and use of language have been reported to be affected by high levels of prenatal alcohol exposure (Mattson & Riley, 1998; Streissguth, Barr, Kogan, & Bookstein, 1996), measurement of language ability has been an important feature of interdisciplinary assessment of these individuals. The preponderance of evidence regarding language behavior in children with an FASD has been gathered using standardized, norm-referenced tests (Abkarian, 1992; Becker, Warr-Leeper, & Leeper, 1990; Carney & Chermak, 1991; Church, Eldis, Blakley, & Bawle, 1997; Church & Kaltenbach, 1997; Gentry et al., 1998; Janzen, Nanson, & Block, 1995; Weinberg, 1997). The goal of these studies has been to establish how well children with an FASD comprehend and/or produce language structures in standardized contexts. Typically, these contexts measure language using discrete responses at or below the level of single-sentence utterances. Although the results have revealed an array of performance deficits, no core deficit profile has emerged.

Because no recognizable deficit profile has resulted from research using standardized language tests, researchers have begun to look at suprasentential discourse in school-aged children diagnosed with an FASD. In preliminary research, discourse level deficits have been documented in children with an FASD including reduced ability to provide sufficient information for listeners both during conversations (Hamilton, 1981) and in narratives (Coggins, Friet, & Morgan, 1998; Coggins, Olswang, Carmichael-Olsen, & Timler, 2003). In addition, caregivers report that children with an FASD often fail to accommodate the perspectives of others during interaction (Timler, Olswang, & Coggins, 2005). This early research suggests that despite widely variable performance on standardized tests, children with an FASD may have difficulty producing integrated extended discourse that requires them to balance linguistic and social–cognitive task demands (Coggins et al., 2003). This emerging profile, when coupled with our ability to identify an FASD independent of communication ability, makes this heterogeneous group of children an ideal population to test the discriminative utility of a narrative analysis system.

Narrative Analysis

As a primary form of extended discourse, narratives provide children with a means of verbally recapitulating experiences (Bishop & Edmundson, 1987; Feagans & Appelbaum, 1986; Feagans & Short, 1984) and are an important source of knowledge about inference, social cognition, and perspective taking (Owens, 1999). The ability to produce contextually integrated extended discourse is difficult to measure using the discrete responses typical of standardized tests. Analysis of narrative samples offers a viable alternative.

Unlike standardized measures, narrative analysis allows for measurement of discourse level parameters of communication that result directly from the pragmatics of a relatively communicative interaction (Owens, 1999). These parameters of behavior manifest in the history of concepts as they are developed across sentences in the narrative text and should provide information regarding language ability that is unavailable in the noncommunicative context of standardized testing. Arguably, the most informative context in which to sample children's narrative ability is one that obligates them to organize and generate narratives without an adult model or other contextual supports (Curenton & Justice, 2004; Juncos-Rabadan, Pereiro, & Rodriguez, 2005; Norbury & Bishop, 2003). This decontextualized narrative discourse stresses the language system by limiting the nonlinguistic tools available during discourse. These limitations determine the type of discourse breakdowns that can be predicted in children with compromised cognitive systems. The Semantic Elaboration Coding System (Thorne, 2004) was designed to capture these predictable discourse level behaviors in school-aged children.

The Semantic Elaboration Coding System

The Semantic Elaboration Coding System implements a framework for narrative analysis based upon cognitive linguistics (Croft & Cruse, 2004; Langacker, 1991; Talmy, 2000b; Tomasello, 2003). *Cognitive linguistics* seeks to account for structural properties of language in terms of its relation to more general conceptual structures and functions. It has, therefore, examined "the linguistic structuring of basic ideational and affective categories attributed to cognitive agents, such as attention, perspective, volition, and intention, and expectation and effect" (Talmy, 2000b, Vol. I, p. 3).

[1]An unpublished training manual for the Semantic Elaboration Coding System is available from the first author via jct6@u.washington.edu.

In a detailed look at the conceptual structuring of narrative, Talmy (2000a) identified a series of conceptual parameters in narrative that constitute a "set of organizing principles that apply in common across all major cognitive systems" (p. 422). The Semantic Elaboration Coding System is organized along two of these parameters that would be expected to vary monotonically with quality in a decontextualized narrative. The first involves the strategic use of linguistic reference to assure that concepts are explicit and uniquely identifiable in the text. The second involves the degree to which semantic concepts are elaborated or well specified in the text.

The strategic use of reference in narrative. In any narrative, it is essential that the concepts involved (both entities and events) are kept distinct from each other to reduce ambiguity. The linguistic strategies used to make distinctive reference to various concepts in a narrative may vary in form from semantically complete phrases and clauses to semantically ambiguous forms like pronouns dependent upon the presuppositions the narrator has about the listener's current knowledge and attention state regarding those concepts. Wong and Johnston (2004) identify three basic *reference functions* in narrative tasks related to presuppositions about the knowledge and attention state of the listener: (a) the *introduction* of new concepts into the discourse (presupposes no knowledge of the concept), (b) the *maintenance* of foreground/in-focus concepts (presupposes both knowledge of and attention to the concept), and (c) the *reintroduction* of previously introduced background/out-of-focus concepts in the discourse (presupposes knowledge of, but limited attention to, the concept). The distinction between adequate and inadequate use of various strategies for meeting these discourse functions cannot be made without consideration of both the textual and extratextual context of the particular instance of use (see Cornish, 1999, for a discussion; see also Levine & Klin, 2001; Maratsos, 1976; van Hoek, 1997; Wong, 2001; Wong, Au, & Stokes, 2004).

In decontextualized narrative discourse, strategies for meeting all three basic reference functions are restricted to the linguistic code (see Halliday & Hasan, 1976). To maintain unambiguous reference, storytellers must use discourse strategies that do not presuppose unwarranted knowledge or attention on the part of their listener or require extralinguistic support to be interpreted meaningfully. This can be particularly challenging for younger storytellers as they continuously adapt their narratives to the ever-changing knowledge and attention states of their listeners (Coggins et al., 1998; Cornish, 1999; Lewis, 2004; Wong & Johnston, 2004).

School-aged children are learning to effectively incorporate a variety of reference strategies into their language production (Stephens, 1988), allowing differentiation between children with typical and delayed language development (see Liles, Duffy, Merritt, & Purcell, 1995; Wong, 2001, for example). Measurement of the strategic use of reference in narrative serves as a primary component of the Semantic Elaboration Coding System.

Semantic elaboration. Decontextualized discourse also demands a greater density of ideas, or *semantic elaboration,* from the storyteller. An analysis of narrative elaboration must account for the contribution of particular words or syntactic structures to the listener's growing conceptualization of a concept in a way that accounts for the history of that concept in the preceding discourse (Croft & Cruse, 2004; Fauconnier, 2004; Klin, Weingartner, Guzman, & Levine, 2004; Talmy, 2000b). This requires that the measurement of elaboration be integrated with the measurement of successful reference to those concepts because a structure cannot contribute to the elaboration of a concept if it does not unambiguously make reference to that concept.

Investigators have heretofore used a variety of lexically based and syntactically based measures to capture elaboration in discourse. These measures have differentiated children with different overall language ability as measured by standardized language tests (Condouris, Meyer, & Tager-Flusberg, 2003; Hammer, Yont, & Tomblin, 2005; Loban, 1976). Most approaches treat the structures they quantify independent of the textual history of the concepts they describe, much as is done with standardized tests of lexical knowledge or syntactic competence. Consequently, they are unlikely to provide information regarding language ability beyond that available through standardized testing (a largely untested assumption, but see Hesketh, 2004). A system that integrates measurement of elaboration and reference strategy may provide information about integrated language abilities that is inaccessible to the more traditional approaches.

Purpose

The Semantic Elaboration Coding System is designed to be used with decontextualized narratives produced for a naive listener by school-aged children as they look through the wordless picture book, *Frog Where Are You?* (Mayer, 1969). It integrates analysis of two narrative discourse parameters that would be difficult to quantify using standardized measures: (a) *ambiguity,* the use of inappropriate strategies of reference, and (b) *elaboration,* the semantic elaboration of concepts as they develop across the narrative (see Thorne & Coggins, 2004; see also Thorne & Coggins, 2005).

With respect to children diagnosed with an FASD, the Semantic Elaboration Coding System must be able to (a) identify children with an FASD who perform poorly on a standardized test to establish a level of concurrent

validity with that standardized test and (b) identify those children with an FASD who perform like typically developing (TD) children on the standardized language test to establish superior classification accuracy when compared with that test. This study was designed to test the potential for the Semantic Elaboration Coding System to make these key discriminations. Specifically, the research questions under study were as follows:

1. Can narrative analysis using the Semantic Elaboration Coding System correctly classify a group of school-aged children into separate groups based on typical development versus an identified FASD?
2. Can narrative analysis using the Semantic Elaboration Coding System accurately predict which children with an identified FASD have either average or low performance on a standardized language task?
3. Which specific measure or combinations of measures from within the Semantic Elaboration Coding System are most accurate in performing these discrimination tasks, and, therefore, reasonably warrant further development?

Method

Participants

Thirty-two school-aged children from two previous studies (Carmichael-Olson & Astley, 2005; Coggins, 1995) participated. They ranged in age from 8;5 years to 11;7 years (M = 9;11 years) and presented a range of socioeconomic and ethnic profiles. Sixteen of the children presented key clinical features consistent with an FASD while the remaining children were considered TD.

Children with an FASD. The 16 FASD participants had a diagnosis of either (a) full or partial fetal alcohol syndrome or (b) a confirmed alcohol exposure accompanying static encephalopathy or neurobehavioral disorder. Diagnosis was performed by an interdisciplinary team at the University of Washington Fetal Alcohol Syndrome Diagnostic and Prevention Network. All children were originally diagnosed using the 1999 version of the 4-Digit Diagnostic Code (Astley & Clarren, 1999). All codes were translated into the 2004 version of the 4-Digit Diagnostic Code (Astley, 2004) to provide an up-to-date diagnostic standard for comparison. Participants reflected "the true diversity and continuum of disability associated with prenatal alcohol exposure" (Astley, 2004, p. 13). Table 1 specifies each participant's 4-Digit Diagnostic Code, which provides information regarding their growth, facial morphology, brain development, and alcohol exposure (see Astley, 2004, for details of code interpretation).

Existing nonverbal and verbal measures provided an additional basis for selection and are also provided in Table 1. The Matrices subtest from the Kaufman Brief Intelligence Test (Kaufman & Kaufman, 1990) provided an overall measure of nonverbal problem solving, with participants excluded based on a score 1.5 standard deviations below the mean (range: 79–130; M = 101). The 16 participants in the FASD group were dichotomized into two performance groups based on their scores from the Re-Creating Sentences subtest of the Test of Language Competence (RS-TLC; Wiig & Secord, 1989): (a) an average-performance group (n = 9) with standard scores within one standard deviation of the mean (between 7 and 10) and (b) a low-performance group (n = 7) with standard scores two or more standard deviations below the mean (between 3 and 4).

The resulting sample included 9 females and 7 males. Family income for the group ranged from $15,000 to $220,000 per annum ($M$ = $88,000, Mdn = $75,000). The group included 11 children identified as Caucasian, 3 as bi- or multiracial, and 1 each as African American and Native American. Only 3 of the children were still living with their biological parent(s) at the time data were collected. The remaining 13 were in adoptive or legal guardianship placements (5 with relatives).

TD peers. Each participant with FASD was paired with a TD peer matched on chronological age (±12 months, mean difference = 3.5 months). Thirteen TD age-matched peers also matched the gender of their FASD counterpart (15 females, 17 males). Table 1 displays age and gender for all participant pairs.

The TD aged-matched peers were recruited from elementary schools representing two school districts in the greater metropolitan Seattle area. Median family incomes were similar across school districts ($61,435–$62,195). The sample included 12 children identified as Caucasian, 2 as Asian, and 1 each as African American and Hispanic (representative of the home county for both districts).

No intelligence or standardized language measures were available for TD participants. However, a school psychologist familiar with the 16 children and with the profile of FASD screened school records for each child with respect to school performance, social ability, and general behavior. Based on this review of available records, each was judged to be following a typical developmental course due to their unremarkable behavior and adequate school achievement. The TD participants did not undergo the same interdisciplinary assessment as the children with FASD.

Materials

Self-generated, decontextualized narratives were selected from two independent databases: one from a study

Table 1. Participant characteristics: diagnosis, language performance group, test scores, age, and gender.

Diagnostic Code & Category[a]	Re-Creating Sentences—Test of Language Competence[b]	Kaufman Brief Intelligence Test—Matrices[c]	FASD Group		TD Group	
			Gender	Age	Gender	Age
2443 = A	3: low	79	F	8;9	F	8;8
1234 = F	3: low	90	M	9;2	M	8;11
3432 = B	3: low	95	F	8;11	F	9;3
2444 = A	3: low	80	M	10;8	M	10;11
4234 = E	4: low	80	F	10;6	M	9;9
4344 = C	3: low	96	M	11;1	M	11;4
1324 = G	3: low	87	F	11;2	M	11;6
1124 = H	7: average	92	F	8;5	F	8;4
1124 = H	7: average	128	M	8;8	M	8;9
1224 = H	7: average	130	M	8;10	M	8;11
3344 = C	7: average	101	M	9;3	M	9;1
1224 = H	8: average	114	F	9;5	F	9;2
1223 = H	9: average	113	F	10;6	F	9;6
1223 = H	9: average	122	F	10;6	F	10;10
1224 = H	7: average	98	F	11;2	M	11;5
3233 = E	10: average	105	M	11;5	M	11;7
Mean	Average: 8; low: 3	101		9;11	9;10	

Note. Diagnostic code provides information, from left to right, regarding growth, facial morphology, brain development, and alcohol exposure. Scores range from 1 (*unremarkable*) to 4 (*severe*). FASD = fetal alcohol spectrum disorder; TD = typical development; F = female; M = male; FASD categories: A = FAS (alcohol exposed); B = FAS (alcohol exposure unknown); C = partial FAS (alcohol exposed); E–H indicate the remaining FASD categories (with confirmed alcohol exposure). Details for interpretation of the 4-Digit Diagnostic Code of FASD can be found in Astley (2004).

[a]Astley (2004). [b]$M = 10$, $SD = 3$. [c]$M = 100$, $SD = 15$.

involving children diagnosed with an FASD (Carmichael-Olson & Astley, 2005) and the second from a normative study of TD school-aged children (Coggins, 1995).

Procedures

All narratives from the two respective databases were elicited using *Frog Where Are You?* (Mayer, 1969). In both studies, participants were tested individually and received the same instructions. Each child was instructed to look through Mayer's book to become familiar with the story line. When the child completed previewing the story, the examiner exhorted the participant to tell the best story possible while using the picture book as a visual prompt. In each case, examiners were seated across the room from the child, with the storybook out of their line of sight.

Transcription and Coding

Narratives were recorded on audiocassette and orthographically transcribed by trained graduate students. The second author supervised the narrative collection and transcription process and then stripped all transcripts of identifying information while assigning each a random code so that relevant information could be retrieved for later data analysis.

Transcripts were coded by the first author using the Semantic Elaboration Coding System (Thorne, 2004). The system assigns codes along the parameters of (a) ambiguity, the consequence of inappropriate reference strategies, and (b) elaboration of concepts.

Ambiguity. Operationally, measurement of ambiguity involved coding references to concepts as either unambiguous or ambiguous. To reduce the number of coding categories, ambiguous anaphoric reference strategies for maintenance and reintroduction of concepts and ambiguous introduction strategies that make unwarranted presuppositions about listener knowledge and attention were collapsed into just two ambiguity categories (nominal and pronominal) because their use has similar impact on a listener's discourse processing (Cornish, 1999; van Hoek, 1997).

Elaboration. Measurement of elaboration involved core lexical items that unambiguously introduced concepts into the story that were coded as either schematic (i.e., minimally characterized) or elaborated. Additional words that helped elaborate concepts were also coded.

For this study, each word in a transcript was assigned 1 of 10 mutually exclusive scoring codes along

these two parameters, or a null code. The 10 scoring codes are presented later with a brief definition of each category. Further details can be found in the Semantic Elaboration Coding System (Thorne, 2004).

Ambiguity codes. Two codes identified unambiguous anaphoric reference to concepts and made a distinction between nominal forms and pronominal forms serving maintenance and reintroduction functions.

1. *Nominal reference (NR):* an unambiguous nominal form used to maintain or reintroduce a concept previously introduced into the discourse (e.g., *a dog* introduced into the narrative later referred to unambiguously as *the dog*).
2. *Pronoun reference (PR):* an unambiguous pronominal form used to maintain or reintroduce a concept previously introduced into the discourse (e.g., *a dog* later referred to unambiguously as *he* or *it*).

Two additional codes were used to identify cases in which reference was ambiguous.

3. *Ambiguous nominal reference (ANR):* an ambiguous use of a nominal form attempting to introduce, maintain, or reintroduce a concept.
4. *Ambiguous pronoun reference (APR):* an ambiguous use of a pronominal form attempting to introduce, maintain, or reintroduce a concept.

Semantic elaboration codes. Six codes were used to quantify semantic elaboration. Four of these codes dichotomized core lexical items as either schematic or elaborated. Two codes identified core lexical units as schematic.

5. *Schematic verb (SV):* a word that introduced basic information regarding an event into the discourse (i.e., the *fact* that something happened: *went, got, is, going*).
6. *Schematic nominal (SN):* a word that introduced basic information regarding an entity into the discourse (e.g., *boy, dog, frog, jar, animal, thing*).

Two additional codes identified those core lexical items that were relatively elaborated.

7. *Elaborated verb (EV):* a word that introduced elaborated information regarding an event into the discourse (i.e., the manner in which something happened: *ran, fell, chased, yelled*).
8. *Elaborated nominal (EN):* a word that introduced elaborated information regarding an entity unambiguously into the discourse (e.g., *Timmy, elk, bullfrog, wife, bumblebee*).

Two final codes identified word forms associated with these core lexical items that provided additional semantic elaboration. These two codes are the most frequent in the Semantic Elaboration Coding System, making up a significant portion of the information the system gathers.

9. *Verb satellite (VS):* a word providing elaborating information about a verb (e.g., went *away,* ran *quickly, in the morning when* he got *up*).
10. *Nominal modifier (NM):* a word providing elaborating information regarding a nominal (e.g., *big mad* owl, frog *that ran away*).

A null code was used to indicate that a word did not fit any of the 10 scoring categories.

Null code (null): a word not meeting operational definitions for any ambiguity or elaboration code category in the system.

Analysis

Intercoder agreement. A graduate student in speech and hearing sciences was recruited and trained to function as a secondary coder. Coder competence was established when intercoder agreement between the primary (the first author) and secondary coder reached a kappa of .7 or better for each code in the system on a set of five training narratives taken from the CHILDES databank (MacWhinney, 2000).

The primary coder then scored all 32 of the study narratives while the secondary coder independently scored 25% of the narratives (n = 8) randomly selected using SPSS for Windows (SPSS, 1998). Random selection and all coding were completed before either coder knew the diagnostic status, age, or gender of the storytellers. The resulting sample contained 5 narratives from the TD group and three from the FASD group.

For both training and study narratives, kappa was calculated as a measure of agreement between coders for each of the 10 Semantic Elaboration Coding System codes and for the null code. Calculation of kappa was conducted separately for each code, with agreement based on a binary decision—every word in the narratives was identified as carrying the designated code or not (following Kraemer, n.d.; see also Bakeman & Gottman, 1997). All words not coded by both judges with the designated code were treated as disagreements in the calculation of kappa for that code. Because it reveals performance for individual codes and avoids overly optimistic and difficult-to-interpret estimates of overall agreement that can occur in multicode calculations of kappa, this is a conservative method of estimating intercoder agreement (Acklin, McDowell, Verschell, & Chan, 2000; see also Kraemer, Periyakoil, & Noda, 2004). Results are presented in Table 2.

Eleven kappa statistics were computed. The precision of 10 kappa scores ranged from substantial (i.e., .6–.8) to almost perfect (i.e., >.8; Kraemer, Periyakoil, & Noda,

Table 2. Interrater agreement (kappa) for all Semantic Elaboration Coding System codes.

Code	κ
VS	.836
SV	.893
EV	.935
NM	.653
NR	.876
SN	.793
EN	.792
PR	.767
ANR	.764
APR	.540
Null (no code)	.836

Note. Calculation of the kappa was conducted separately for each code, with agreement based on a binary decision: Every word in the narratives was identified as carrying the designated code or not. All words not coded by both judges with the designated code were treated as disagreements in the calculation of the kappa for that code. VS = verb satellite; SV = schematic verb; EV = elaborated verb; NM = nominal modifier; NR = nominal reference; SN = schematic nominal; EN = elaborated nominal; PR = pronoun reference; ANR = ambiguous nominal reference; APR = ambiguous pronoun reference.

2004; Landis & Koch, 1977). The kappa statistic for the coding of ambiguous pronoun reference was in the moderate range of precision (i.e., .4–.6). Because it increases chances of Type II error, the moderate level of intercoder agreement on this single code might be considered insufficient for clinical application (cf. Bakeman & Gottman, 1997; Cicchetti & Sparrow, 1981), highlighting the need for attention to coder training and measurement stability in subsequent development of the system (see the Discussion section for more on pronouns and intercoder agreement).

Data preparation. Several preparatory steps were taken to ready the data for analysis. First, the total number of words (TW) was calculated for each narrative (excluding mazes, range: 154–796; M = 308) using SALT (Miller, 2004). Second, the raw frequencies of each of the 11 scoring codes in the 32 narratives were calculated also using SALT. Next, the raw frequencies of codes for APR and ANR were combined to create a summary ambiguity score, while the raw frequencies of codes for EV forms, EN forms, VS forms, and NM forms were combined to create a summary elaboration score.

Next, code and score rates were computed by dividing each measure by the TW in the narrative. Because the Semantic Elaboration Coding System examines narratives on a word-by-word basis, the TW in a story was considered to best represent the length of the story and thereby became the denominator used in the calculation of code and score rates. Using a common denominator for the calculation of all rates also facilitated comparison between rates.[2] This process resulted in 26 narrative measures for analysis: 11 code frequencies, 2 summary scores, and 13 associated rates as a function of narrative length. Table 3 presents all 26 measures.

Classification accuracy analysis. To explore the accuracy of classification for each of the 26 measures, empirical classification rates including sensitivity (true positive rate), specificity (true negative rate), and efficiency (overall accuracy rate) were examined. Methods from signal detection theory based on these three measurement parameters were implemented to judge the relative potential of each of the 26 measures to match the classification of participants provided by the appropriate reference standard (Kraemer, 1988, 1992; Kraemer, Noda, & O'Hara, 2004; McFall & Treat, 1999). The two classifications of particular interest were as follows: *Classification 1*—the accuracy of each measure in classifying participants as members of the FASD or TD group; *Classification 2*—the accuracy of each measure in classifying participants diagnosed with an FASD as a member of the group with average performance or low performance on the RS-TLC.

More specifically, for both classifications, each of the 26 measures was analyzed using an empirical receiver operating characteristics (ROC) curve based on values obtained from the 32 narratives (for recent applications of this method, see Dwolatzky et al., 2003; see also Heilmann, Weismer, Evans, & Hollar, 2005). This analysis compared the classification of each measure against the classification by the appropriate reference standard, and provided an ROC curve plotting the sensitivity against 1 minus the specificity of each measure for all obtained values. The ROC curve, the area under the ROC curve (AUC), and the asymptotic significance, standard error, and 95% AUC confidence intervals were all calculated using SPSS.

Results

Criteria for a Reasonable Measure

The AUC is a widely accepted measure of overall accuracy (McFall & Treat, 1999). An index of effect size, the AUC can distinguish between tests that are random (AUC = 0.5), poorly accurate (0.5–0.7), moderately

[2]It is common to calculate proportional rates for referential terms based on total number of referential opportunities rather than total words. In the case of the Semantic Elaboration Coding System, this would mean dividing each ambiguity code frequency by the total number of NRs + PRs + ANRs + APRs + SNs + ENs. To assure that results using total word rates were not substantially skewed when compared with those using total opportunity rates, correlations and ROC curves were run for ambiguity code rates calculated using both methods. Rates were substantially correlated ($r > .9$), and AUC results were not significantly different ($p > .4$). AUC data are reported using rates calculated with TW to facilitate comparison between elaboration rates and ambiguity rates.

Table 3. Semantic Elaboration Coding System measures evaluated for classification accuracy.

Raw Code Frequencies	Summary Scores and Formula	Rates as a Function of TW
Ambiguity measure		
NR		NR/TW
PR		PR/TW
ANR		ANR/TW
APR		APR/TW
	AS = ANR + APR	AR = AS/TW
Elaboration measure		
EV		EV/TW
EN		EN/TW
VS		VS/TW
NM		NM/TW
	ES = EV + EN + VS + NM	ER = ES/TW
Schematic code		
SV		SV/TW
SN		SN/TW
Null		Null/TW

Note. TW = total words; AS = ambiguity score; AR = ambiguity rate; ES = elaboration score; ER = elaborate rate; Null = no code.

accurate (0.7–0.9), and highly accurate (0.9–1.0; see Swets, 1988). To be considered reasonable in the current analysis, a measure required an AUC with an asymptotic significance better than .02 and an AUC 95% confidence interval with a lower bound above 0.7. These criteria assured not only that the AUC was significantly different from a random test (i.e., AUC = 0.5) but also that it had at least a moderate chance of accurately classifying cases.

Sensitivity, specificity, and efficiency values were calculated at the best possible cut-points for measures obtaining an AUC with an asymptotic significance better than .02. A "best cut-point" was defined as the obtained value along the ROC curve with the highest efficiency (overall accuracy rate). If multiple cut-points had equivalent efficiency, the one with the highest sensitivity was chosen.

Data Presentation

Figure 1 presents AUC data for both of the tested classifications. The top portion of Figure 1 displays results for Classification 1—FASD versus TD group membership. The lower portion of Figure 1 displays results for Classification 2—performance grouping for the FASD participants: low performance versus average performance on the RS-TLC. Figure 1 includes asymptotic significance levels, AUC values, and 95% confidence intervals for each measure (i.e., test) that achieved an asymptotic significance better than .02 for each classification. The shaded regions of Figure 1 indicate the range used to determine that a particular test's confidence interval indicated reasonable accuracy. The four measures that reached the criteria for a reasonable measure are indicated by a double asterisk. Those measures not included on Figure 1 were not statistically different from a random test.

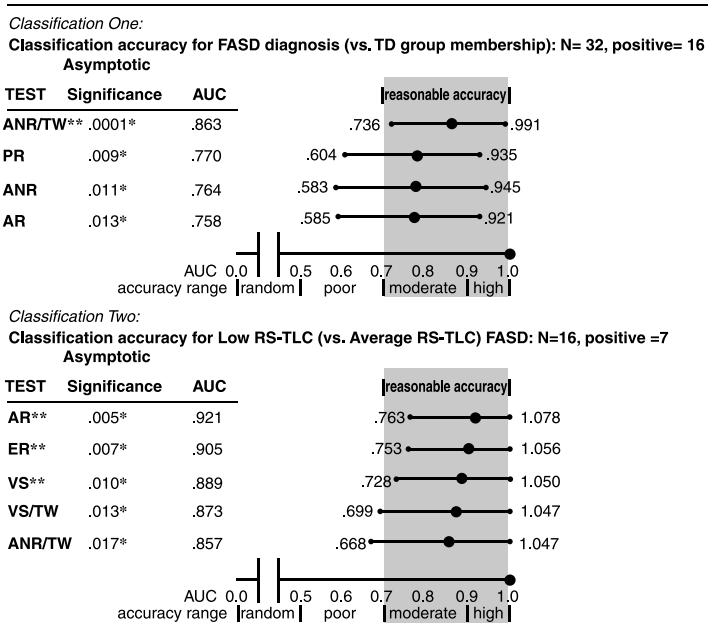
Table 4 displays information on the sensitivity, specificity, and efficiency at the best cut point for the most promising measures. These measures were chosen based on visual inspection of ROC curve shape (see Kraemer, 1992). The top of Table 4 includes data for Classification 1—TD versus FASD, while the lower portion displays data for Classification 2—RS-TLC performance group.

Accuracy for Classification 1—FASD Versus TD Group Membership

As can be seen in the top portion of Figure 1, the rate of ambiguous nominal reference (ANR/TW) obtained an AUC of .863, asymptotic significance = .0001. This AUC indicates classification accuracy solidly within the moderate-to-high accuracy range with a 95% confidence interval from .736 to .991.

As revealed in Table 4, the rate of ambiguous nominal reference (ANR/TW) achieves strong sensitivity, specificity, and efficiency for Classification 1. At the best possible cut point, >.0165 (i.e., greater than 1.65% of total words being ambiguous nominal references equals a positive test for FASD status), ANR/TW achieved a sensitivity of 87.5%, a specificity of 75%, and overall efficiency of 81.25%. At this particular cut point, it correctly

Figure 1. Area under the receiver operating characteristic (AUC) curve with 95% confidence intervals for measures asymptotically different than a random test. Analysis compares classification by Semantic Elaboration Coding System measures indicated and that by reference standard. For Classification 1, reference standard is diagnosis of an FASD by interdisciplinary team. For Classification 2, reference standard is based on average performance (within 1 *SD* of the mean) or low performance (< −2 *SD* below the mean) on the Re-Creating Sentences subtest of the Test of Language Competence (RS-TLC). FASD = fetal alcohol spectrum disorder; ANR = ambiguous nominal reference; TW = total words; PR = pronoun reference; AR = ambiguity rate; ER = elaboration rate; VS = verb satellite. *Asymptotic significance better than .02. **Reasonable test based on a lower bound of AUC confidence interval above 0.7. All values generated with SPSS.



classified 14 of 16 children from the FASD group and 12 of 16 from the TD group.

Post hoc analysis of ANR coding revealed that nominal references were most likely to be rated ambiguous when definite nominal forms were used to introduce or reintroduce concepts (>92% of 185 ambiguous nominal references). In a concordance search of all 32 stories, only 14 (<8%) nominals out of 185 that were rated ambiguous contained the indefinite articles *a* or *an*. Of these 14, 8 were in stories told by children with a diagnosis of FASD and 6 were in stories told by children in the TD group.

As seen in the top portion of Figure 1, the raw frequency of two codes, PR and ANR, achieved a significant point estimate of AUC in the moderately accurate range. However, both measures have AUC confidence intervals that fall below the criteria of .7 set for a reasonable measure. Because the calculation of the ROC curve is based on fewer values, the width of a confidence interval for AUC increases with smaller sample sizes and greater numbers of participants with tied scores. Both ANR and PR codes resulted in large numbers of tied scores relative to sample size. Twenty-nine participants shared their ANR frequency with at least 1 other participant, while 20 shared their PR frequency with at least 1 other participant. As a result, these measures had wide 95% confidence intervals for AUC that ranged below the criteria (see Figure 1). Notice in Table 4, however, that at its best cut-point, ANR was highly sensitive, specific, and efficient for Classification 1, correctly classifying 13 children from each group. While PR correctly classified an equal number from the FASD group, its relatively poor specificity makes it a less promising measure.

Accuracy for Classification 2—RS-TLC Performance for Participants With an FASD

AR, ER, and VS met study criteria for reasonable measures with high classification accuracy. As can be seen in the lower portion of Figure 1, a high AUC was

Table 4. Sensitivity, specificity, and efficiency of most promising measures at their best cut-point for both Classification 1 and Classification 2.

Measure	Cut-Point	Sensitivity(%)	Specificity(%)	Efficiency(%)
Classification 1: FASD vs. TD group membership				
ANR/TW	>.0165	87.50	75	81.25
PR	≤18.0	81.25	62.50	71.88
ANR	>5.0	81.25	81.25	81.25
Classification 2: RS-TLC performance group (FASD only)				
AR	>.0588	85.7	100	93.75
ER	≤0.4816	71.4	100	87.50
VS	≤89.0	100	66.7	81.25

Note. Best cut-point chosen as most efficient test weighing sensitivity over specificity for equally efficient tests. High sensitivity and a negative test help rule out diagnosis, which is useful for screening. High specificity and a positive test help to confirm a diagnosis. Higher efficiency indicates better overall diagnostic performance. RS-TLC = Re-Creating Sentences subtest of the Test of Language Competence.

achieved for the AR. The obtained value of .921, asymptotic significance = .005, places this result in the highly accurate range, with a 95% confidence interval ranging from .763 to 1.00. The lower portion of Table 4 shows that at the best cut-point, >.0588 (i.e., more than 5.88% of words being ambiguous indicates low RS-TLC performance group), this measure obtained a sensitivity of 85.7%, a specificity of 100%, and an efficiency of 93.75%. At this cut-point, the measure accurately classified 6 of 7 children in the low RS-TLC performance group and all 9 of those in the average RS-TLC performance group.

The AUC of the ER, as shown in the lower portion of Figure 1, is .905, asymptotic significance = .007. This AUC falls in the highly accurate range, with a 95% confidence interval ranging from .753 to 1.00. As seen in lower portion of Table 4, at the best cut-point, ≤.4816 (i.e., 48.16% or less of words being elaborators indicating low RS-TLC performance group), ER obtained a sensitivity of 71.4%, a specificity of 100%, and an efficiency of 87.5%. At this cut-point, the measure accurately classified 5 of 7 children in the low RS-TLC performance group and all 9 of those in the average RS-TLC performance group.

The total number of VS met study criteria for Classification 2. As can be seen in the lower portion of Figure 1, this measure obtained an AUC of .889, asymptotic significance = .01, placing it in the top of the moderately accurate range with a 95% confidence interval ranging from .728 to 1.00. The lower portion of Table 4 shows that at the best cut-point, ≤89 (89 or fewer VS indicating low RS-TLC performance group), this measure obtained a sensitivity of 100%, a specificity of 66.7%, and an efficiency of 81.25%. At this cut-point, the measure accurately classified 7 of 7 children in the low RS-TLC performance group and 6 of 9 children in the average RS-TLC performance group. This measure's high sensitivity but relatively modest specificity limits its diagnostic utility to that of a potential screening measure.

Combination of Classifiers

Based on their complementary distribution of classification errors, a combination of ER and AR was tested in a post hoc analysis to determine if combining these measures would improve classification accuracy for Classification 2. The two summary rates were combined using an *or* rule. A positive classification as belonging to the low RS-TLC performance group was obtained if a child had an ER less than or equal to 48.16% or an AR greater than 5.88%. This combination of measures perfectly predicted low RS-TLC performance group (vs. average RS-TLC performance group) with 100% sensitivity, specificity, and efficiency.

Discussion

This study investigated the classification accuracy of 26 measures generated using a new narrative analysis tool. The investigators explored ROC curves to identify the classification capabilities of the Semantic Elaboration Coding System as compared with two reference standards: (a) an interdisciplinary team diagnosis of an FASD and (b) performance grouping based on scores from a standardized expressive language measure, the RS-TLC (Wiig & Secord, 1989). The results are discussed for each topic in turn beginning with classification based on the performance of children with FASD on the RS-TLC.

Concurrent Validity of the Semantic Elaboration Coding System

The degree of elaboration a child uses in narrative discourse is a developmental skill (see Curenton & Justice, 2004; Eisenberg & Gillam, 2005; Loban, 1976; Scott, 1988) that is predictive of language impairment (see Greenhalgh & Strong, 2001; Johnston & Kamhi, 1984). Our results support these findings. The ER was a reasonable and highly accurate predictor of poor performance on the RS-TLC for school-aged children with FASD. At its best cut-point, ER was able to match classification based on the RS-TLC for 14 of 16 children (87.5%) into either low RS-TLC performance or average RS-TLC performance groups. In addition, we found that the summary AR was also a reasonable and highly accurate classifier of language performance group. At its best cut-point, AR matched the classification based on the RS-TLC for 15 of 16 children (93.75%). Post hoc analysis indicated that a logical combination of these two measures using

an *or* rule correctly classified all 16 children with respect to their performance on the RS-TLC.

These results support the notion that narrative analysis should play an important role in diagnostic decision making. Classification using information from a narrative analysis perfectly matched that based on performance on a standardized measure of expressive language. Testing of the Semantic Elaboration Coding System against a wider range of standardized language measures to establish a better understanding of its concurrent validity appears warranted.

Classification Accuracy for FASD Diagnosis

A second goal of this feasibility research was to determine whether the Semantic Elaboration Coding System would provide the information needed for a more accurate classification than the standardized measure to support the idea that narrative analysis provides a more ecologically valid description of a child's ability to produce meaningful language in socially integrated discourse. This is clearly shown with the results of our between-groups classification.

One ambiguity measure satisfied strict accuracy criteria in matching the reference standard classification of study participants into FASD and TD groups. The rate of ANR (calculated as a function of narrative length) accurately identified participants previously identified by an interdisciplinary team as having an FASD regardless of the participant's performance on a standardized expressive language task. At its best value, the rate of ANR matched the interdisciplinary team classification for 14 of 16 (87.5%) children with an FASD, and identified 12 of 16 (75%) children with typical development. Moreover, this measure achieved a substantially reliable kappa statistic (κ = .764).

This finding is arguably the most important from the current study. The data demonstrate a procedure for reliably quantifying meaningful performance differences in the use of reference strategies that has the potential to be diagnostically informative for a population of children who have resisted easy classification using standardized language tests. In spite of the FASD group's wide range of cognitive and linguistic abilities, a single narrative measure keyed to the rate at which a child used inappropriate nominal reference strategies was able to match an interdisciplinary team diagnosis of an FASD for all but 2 children.

Ambiguous Nominal Reference by Children in the FASD Group

A closer look at the post hoc analysis of ambiguous nominal reference sheds light on the behaviors children in the FASD group were using in their narratives that was captured by the ANR code. For a reference to be rated ambiguous in the Semantic Elaboration Coding System, an equivocal word choice must occur. In other words, the storyteller has selected a word that fails in its mission to either introduce or unambiguously reference a concept. There are three basic conditions under which a nominal reference may be considered ambiguous in the coding system.

In Condition 1, an existing concept (e.g., THE BOY) is treated as if it were new by using an indefinite nominal form (e.g., *a boy*) to maintain or reintroduce it. Condition 1 involves pragmatically inappropriate use of an indefinite nominal. Post hoc analysis found this type of error to be rare (<8%) and evenly distributed between the TD and FASD groups. In Condition 2, ambiguity results during reintroduction or maintenance of a concept when the storyteller treats a nominal form new to the discourse as referentially equivalent to a form used previously in the discourse when, in fact, the two are not referentially equivalent. In Condition 3, ambiguity results when a new concept is treated as if it were familiar or already existing in the discourse by using a definite nominal to introduce it into the discourse (e.g., *the boy* used to introduce THE BOY or *the barking* used to introduce an event, BARKING). Conditions 2 and 3 both involve pragmatically inappropriate use of a definite nominal form. It was this inappropriate use of definite nominal forms for introduction, maintenance, or reintroduction of concepts that most commonly (>92%) led to a nominal reference being judged as ambiguous. Condition 2 is considered in detail first.

When children use a particular reference word, they are, in essence, making a categorical decision. That is, they are deciding that a particular entity (e.g., the glass container holding the boy's frog in Mayer's, 1969, story) is a member of a category that can be named with a particular nominal form, for example, *jar*. Certainly, *jar* is not the only possible name that could be used to reference the concept GLASS CONTAINER HOLDING FROG. It could reasonably be referred to as a *glass container* or a *glass frog holder,* for example. If the form *jar* is chosen, however, it will be the form used by listeners as the basis for their understanding of the concept GLASS CONTAINER HOLDING FROG.

Decontextualized narratives obligate the storyteller to find linguistic strategies for keeping entities and events distinct. Heim (as cited by van Hoek, 1997) likened each initial reference within a story to a file card that is introduced into a file catalogue (the narrative discourse). In this scheme, subsequent references to a particular event or entity access and potentially update the information on the appropriate file card (cf. Fauconnier, 2004; Levine & Klin, 2001). The pragmatics of English allow specific linguistic strategies to introduce new file cards

into decontextualized discourse (indefinite forms) that are distinct from those for accessing (i.e., maintaining or reintroducing) file cards already present in the discourse (definite nominals and pronouns; see Croft, 2001; Klin et al., 2004; Langacker, 1991; Maratsos, 1976; van Hoek, 1997; Wong & Johnston, 2004).

Applying this analogy, if *jar* is used to introduce the entity concept GLASS CONTAINER, it will be the nominal form listed first on the listener's file card for that concept. It is not the only lexical form available on the file card, but it will be the one that most effectively refers to the concept. When storytellers who have introduced the concept into the story with the nominal complex *a jar* decide to maintain or reintroduce that same concept using a different nominal form, let's say *the bottle,* they are acting ostensively as if their listener will recognize the overlapping nature of JAR and BOTTLE (both are glass containers) and will assign reference appropriately. However, context plays a significant role in when and how the quite distinct categories JAR and BOTTLE are equivalent and when they are not.

In a shared visual context in which only one item fitting in the category GLASS CONTAINER is seen, visual information aids the listener in disambiguating a reference to that glass container whether the term *jar* or *bottle* is used. In a decontextualized discourse, however, that visual information is unavailable to the listener (despite being available to the storyteller). With only their developing conception of the entities involved in the story to support inferences about the referent, listeners may not be able to quickly and easily determine if *the bottle* being referred to is the same GLASS CONTAINER as *the jar* introduced into the story earlier.

When this occurs, a storyteller who has visual support has not recognized the potential increase in processing demands that a switch in reference forms causes for the listener who does not have access to that visual support (Wong & Johnston, 2004). This increased processing effort may or may not lead to an equivalent understanding of the concepts in the story as listeners attempt to find the most efficient way to resolve the ambiguity. Because this switching of reference forms would not create an equivalent difficulty for a listener who shared the visual context, we refer to this reference strategy as *picture-bound reference* (following Shapiro & Hudson, 1991).

A picture-bound reference strategy is even more apparent in Condition 3, in which new concepts are introduced as if they already existed in the discourse. When there is a shared visual context, picture-bound reference is a reasonable and pragmatically appropriate strategy for introducing concepts because visual information will support listeners as they quickly and easily disambiguate the reference. There is not an obligation to verbally introduce concepts into the discourse if they can be introduced visually.

In decontextualized narrative discourse, the visual information is not available to the listener. So, storytellers who use picture-bound reference strategies to introduce concepts are not recognizing the increased processing demands they are placing on their listeners and are risking that their listeners will not develop an equivalent understanding of the concepts in the story. By identifying this picture-bound reference strategy, the Semantic Elaboration Coding System was able to substantially match interdisciplinary team classification of children into the group with an FASD independent of the child's performance on a standardized expressive language task.

Pronouns and Picture-Bound Referencing

As a definite form, pronouns have the potential to be markers of picture-bound reference. Our results, however, do not show ambiguous pronoun reference to be a reasonable measure for accurately classifying children. It may be that pronouns represent a more complex reference form providing for more fine-grained manipulation of listener attention than full nominal phrases (Gundel, Hedberg, & Zacharski, 2001). As relatively complex forms, it is more likely that pronominal forms will be used in error by children in this age group (cf. Schelletter & Leinonen, 2003; van Der Lely, 1997; Wigglesworth, 1997; Wong & Johnston, 2004). This may be seen in the relatively poor specificity of PR in Table 4. Results indicate that despite the fact that the children in the FASD group tended to use relatively few unambiguous pronoun references, the same can be said for many of their TD peers, leading to a relatively high rate of false-positive classifications. The poor classification accuracy of APR may also reflect the fact that, unlike PR ($\kappa = .767$), APR was relatively difficult for judges to agree upon ($\kappa = .540$). Lower precision in a measure results in a higher chance of a Type II error and potentially masks the utility of the underlying construct. Given the uncertainties, this study highlights the need to consider nominal and pronominal lexical forms separately in narrative research but does not diminish the need for continued study of children's development and use of pronominal forms of reference in discourse.

Conclusion

Whether they exhibited average or low performance on a standardized language measure, children in this study who had an existing interdisciplinary team diagnosis of a disorder on the fetal alcohol spectrum (FASD) were more likely than were their typically developing peers to use a picture-bound reference strategy during storytelling. This strategy could be identified with reasonable accuracy using the rate of ANR calculated as a function of narrative length as defined in the Semantic Elaboration Coding System. If this result can be replicated in a

well-designed validation study, the rate of ANR has the potential to provide useful diagnostic information to clinicians trying to identify clinical populations independent of their performance on standardized measures of expressive language.

As measured by the Semantic Elaboration Coding System, both pragmatically inappropriate reference strategies and semantic elaboration demonstrated the potential to play a role in the diagnosis of FASD by identifying languages behaviors that may be quite prevalent in this population (i.e., picture-bound referencing and unelaborated concepts in decontextualized narratives). It is unlikely that these impairments are specific to FASD (see Bates, 2004). Given that both semantic and pragmatic language ability are frequently compromised in children with complex clinical profiles of diverse etiology, these results also point to the possibility that narrative analysis using the Semantic Elaboration Coding System may have utility in other contexts. In particular, the rate of ANR in a narrative, which is easy to compute and has excellent reliability, may be a potential tool for reliably identifying pragmatic deficits in children who perform well on standardized language tasks despite poor performance during the socially integrated discourse of everyday communication.

Limitations of the Current Study

The TD participants in this study did not undergo the same interdisciplinary assessment as did the children with an FASD. TD participants were chosen because records indicated unremarkable behavior and adequate school achievement—a profile that would not, in a clinical setting, trigger such an assessment. This is not the same as undergoing the comprehensive assessment but provides a reasonable basis for contrasting the two groups in the context of a feasibility study. The lack of objective measures confirming that these children were indeed "typically developing" and not subject to a prenatal alcohol exposure increases the risk of Type II errors (potentially masking reasonable measures). The lack of objective language and cognitive measures on these children increases the chances of Type I errors in the unlikely event that as a group, their ability was significantly above average along the parameters of interest (potentially enhancing the apparent differences between the groups). Both of these limitations enhance the need for the results of this initial feasibility research to be confirmed with validation research.

Also, although strict criteria were used to screen out potentially useless test measures in this feasibility study, numerous measures were examined, so our results may be overfitted to the study population. Consequently, any measure and, particularly, any specific cutoff value reported here will need to be confirmed and validated in subsequent research. Results of this feasibility research can point to potentially useful diagnostic or screening measures, but until these measures have been shown to perform similarly in a well-designed validation study, their utility remains potential but unproven.

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Responding to the Challenge of Early Intervention for Fetal Alcohol Spectrum Disorders

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Prenatal alcohol exposure can lead to significant neurodevelopmental disabilities, now recognized as fetal alcohol spectrum disorders (FASD). This includes both fetal alcohol syndrome, a lifelong birth defect, and a wider range of enduring learning and behavior deficits often called alcohol-related neurodevelopmental disorder (ARND). Diagnostic classification systems have been developed to identify children with FASD, and early interventionists from multiple disciplines can be central in identification and referral for diagnosis, and in providing the known protective influence of intervention early in life. With the recent federal mandates to better address needs of children born prenatally affected by substances, or those impacted by abuse and/or neglect, by referring them for screening and possible early intervention services, there is heightened need for providers to understand FASD. There is a growing body of research data describing the teratogenic effects of alcohol on central nervous system function and physical development, the diversity of children with prenatal alcohol exposure and their families, and the developmental and behavioral characteristics of this clinical population. This article reviews the latest research evidence, bearing in mind what is important to early intervention. This article also gives practical guidance on FASD prevention, methods for early screening, and referral of young children for diagnosis of FASD (and referral for needed services once diagnosed), and how to provide education, support, advocacy assistance, and anticipatory guidance for families raising children with FASD. **Key words:** *early diagnosis and intervention*, *fetal alcohol syndrome, alcohol-induced disorders (nervous systems)*, *maternal exposure*, *teratogen*

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PRENATAL ALCOHOL EXPOSURE can lead to significant developmental disabilities, now recognized under the umbrella term of "fetal alcohol spectrum disorders" (FASD) (National Organization on Fetal Alcohol Syndrome, 2004). The number of children with the full "fetal alcohol syndrome" (FAS) has been estimated to be 0.5 to 3 per 1000 live births, with higher rates in some communities (Stratton, Howe, & Battaglia, 1996). But FAS is found in only a fairly small proportion of children affected by prenatal alcohol exposure. Many children have alcohol-induced impairments that can be just as serious, or more so, than those seen in FAS (Mattson, Riley, Gramling, Delis, & Jones, 1998). The term "alcohol-related neurodevelopmental disorder" (ARND) has been applied to this condition (National Institute on Alcohol Abuse and Alcoholism [NIAAA],

2000). Prevalence rates of the full range of FASD beyond FAS, including ARND and other alcohol-related birth defects, are believed to occur about 3 times as often as FAS. A rate of 2 to 6 per 1000 (Centers for Disease Control and Prevention [CDC], 2007), and approach the latest estimated prevalence of autism spectrum disorders. New regulations at the federal level, under both the Keeping Children and Families Safe Act of 2003, which amended and reauthorized the Child Abuse Prevention and Treatment Act (CAPTA), and the Individuals with Disabilities Education Improvement Act of 2004, require that children involved in substantiated cases of child abuse and neglect be referred to early intervention systems. IDEA further requires early intervention referral for children whose development is impacted by prenatal substance exposure. These regulations are certain to result in increased numbers of children in early intervention systems who need referral for FASD diagnosis followed by tailored early intervention.

Clearly, FASD is an important problem that every early interventionist will encounter—now more than ever—and potentially play a key therapeutic role. To help guide practice in early intervention, this article summarizes current research on FASD and provides practical ideas about prevention, qualifying children for services, supporting families, anticipatory guidance, and a developmental systems model useful in thinking about assessment and intervention for young children with FASD.

ALCOHOL AS A TERATOGEN AND FASD PREVENTION

As a neurobehavioral teratogen, alcohol interferes with normal fetal growth and development through multiple actions at different sites. Researchers are now studying the biochemical mechanisms underlying alcohol's effects, in hopes that pharmacologic treatments might eventually be used to intervene with (or prevent) alcohol-related fetal injury. Researchers are also looking at neuroimaging and physical measures (such as EEGs) to understand more precisely how alcohol damages the brain (NIAAA, 2000). Most important to early interventionists is the fact that prenatal alcohol exposure can significantly compromise central nervous system (CNS) function, leading to a wide range of developmental, learning, and behavior problems. These problems can affect later life success. Indeed, natural history data so far show that individuals with FASD have a very high likelihood of suffering secondary disabilities of lifestyle and daily function in adolescence and adulthood (Streissguth et al., 2004).

Fetal effects of alcohol exposure differ depending on the amount, timing, and pattern of maternal drinking, so deficits are highly variable from one child to another. In general, the more a pregnant woman drinks, the greater the severity of persistent neurobehavioral deficits. Episodic (or binge) drinking that creates higher maternal peak blood alcohol concentrations is associated with greater fetal damage. On an individual basis, however, *any* amount of drinking during pregnancy can cause harm, and alcohol use *at any time* during gestation is associated with a higher risk of CNS dysfunction. Figure 1 provides highlights from the 2005 U.S. Surgeon General's Advisory on Drinking and Pregnancy (2005). Early interventionists can advance the important goal of FASD prevention by providing this information to the many women with whom they work who are thinking about pregnancy or are already pregnant, and to women's partners.

IDENTIFYING THE PROBLEM AND QUALIFYING CHILDREN FOR SERVICES

Table 1 defines diagnoses on the fetal alcohol spectrum, and Figure 2 shows the "face" of FAS. These diagnoses are medical conditions. Current practice guidelines suggest that diagnosing physicians work with a multidisciplinary team and follow well-defined FASD diagnostic guidelines. National diagnostic guidelines have been published in the United States for FAS (National Center

- Alcohol consumed during pregnancy increases the risk of alcohol-related birth defects, including growth deficiencies, facial abnormalities, central nervous system impairment, behavioral disorders, and intellectual development.
- No amount of alcohol consumption can be considered safe during pregnancy.
- Alcohol can damage a fetus at any stage of pregnancy. Damage can occur in the earliest weeks of pregnancy, even before a woman knows that she is pregnant.
- The cognitive deficits and behavioral problems resulting from prenatal alcohol exposure are lifelong.
- Alcohol-related birth defects are completely preventable.
- For these reasons:

1. A pregnant woman should not drink alcohol during pregnancy.
2. A pregnant woman who has already consumed alcohol during her pregnancy should stop in order to minimize further risk.
3. A woman who is considering becoming pregnant should abstain from alcohol.
4. Recognizing that nearly half of all births in the United States are unplanned, women of childbearing age should consult their physician and take steps to reduce the possibility of prenatal alcohol exposure.
5. Health professionals should inquire routinely about alcohol consumption by women of childbearing age, inform them of the risks of alcohol consumption during pregnancy, and advise them not to drink alcoholic beverages during pregnancy.

Figure 1. Highlights of the 2005 surgeon general's advisory on drinking and pregnancy. From http://www.surgeongeneral.gov/pressreleases/sg02222005.html.

on Birth Defects and Developmental Disabilities [NCBDD], 2004) and in Canada for the broader spectrum (Chudley et al., 2005). More specific FASD diagnostic systems have been developed for clinical and research use which provide a method for diagnosing the full range of conditions that make up the fetal alcohol spectrum.

FASD diagnoses commonly co-occur with developmental delays or deficits arising from other genetic or medical causes, psychiatric disorders (such as ADHD), and/or academic problems. A full understanding of an individual child's problems requires taking all co-occurring conditions into consideration. Diagnoses on the fetal alcohol spectrum typically add an important dimension to the description of a child's problems as classified by other medical and psychiatric diagnoses generated through the use of diagnostic systems such as *ICD-10* (World Health Organization, 2005), DC:0-3-R (Zero to Three, 2005), or *DSM-IV* (American Psychiatric Association, 1994). Knowing that a child has ADHD in the presence of FASD, for example, can mean that commonly used interventions for ADHD will not have expected effects, and that a different combination of treatment techniques may be required. Indeed, an understanding that a child has neurological unpairment arising from alcohol exposure can fundamentally change a parent's or provider's perception of the child's behavior.

Current FASD diagnostic guidelines usually require evidence of structural, neurologic, and/or functional damage of the CNS. Evidence of structural/neurologic damage may include such findings as microcephaly (small head size), abnormal neuroimaging, or seizure disorders. These can sometimes be identified early in life. Evidence of CNS dysfunction includes standardized test scores that document significant global delays or, more commonly, variability revealed in significant gaps in skills, atypical patterns of development, or uneven profiles of learning strengths and weaknesses. Unfortunately, it is often difficult to gather clear evidence of CNS dysfunction at a young age. Early developmental deficits of alcohol-exposed children may be subtle and yet important precursors of later problems. Tests used with young children often cannot detect variability in learning profiles or subtle problems, so young children

Table 1. Criteria for diagnosing fetal alcohol spectrum disorders*,†

Diagnosis	Diagnostic features
Fetal alcohol syndrome (FAS)	Growth deficiency: *Height or weight less than 10th percentile* Cluster of characteristic minor facial anomalies: *Small palpebral fissures (eyeslits), thin upper lip, smooth philtrum (groove above the upper lip)* Central nervous system damage (evidence of structural and/or functional brain impairment) Reliable evidence of confirmed prenatal alcohol exposure: Not necessary if the cluster of characteristic facial features is fully present
Partial FAS (PFAS)	Some of the characteristic minor facial anomalies Growth deficiency: *Height or weight less than 10th percentile* Central nervous system damage (evidence of structural and/or functional brain impairment) Reliable evidence of confirmed prenatal alcohol exposure
Alcohol-related neurodevelopmental disorder (ARND)	Central nervous system damage (evidence of structural and/or functional brain impairment) Reliable evidence of confirmed prenatal alcohol exposure

*Adapted from the Astley (2004).

†The 4-Digit Diagnostic Code (Astley, 2004) is a system used by clinicians and researchers to evaluate the effects of prenatal alcohol exposure. While the 4-Digit Code maps onto these widely known diagnoses, the system actually uses different descriptive terms to more precisely describe *how* children manifest PFAS and ARND. There are other diagnostic guidelines that also include a category called "Alcohol-Related Birth Defects" (ARBD). ARBD exist in the presence of confirmed prenatal alcohol exposure, but children who have ARBD do not necessarily show the characteristic facial features. ARBD are defined as follows: "Any of a number of anomalies (such as heart or kidney defects) present at birth that are associated with maternal alcohol consumption during pregnancy" (NIAAA, 2000, p. 286).

will less often meet FASD diagnostic criteria. In addition, because alcohol effects may often emerge most clearly as deficits in higher level cognitive functions, children's problems may not even become evident until well past the window for early intervention, around second to fourth grades (Olson, Morse, & Huffine, 1998b). Yet there is growing knowledge about the plasticity of the CNS, and intriguing findings on the positive developmental effects of enriching the motor and learning environment with alcohol-exposed animals (eg, Klintsova, Goodlet, & Greenough, 1999; Miura, Whinery, Dominguez, Riley, & Thomas, 2005). These strongly imply that early identification and intervention for children who are alcohol-exposed may be especially important, because CNS function might potentially be improved.

Some states recognize the full FAS as a diagnosed condition with a high probability of developmental delay, thus deserving early intervention. But there are many additional children impacted by prenatal alcohol exposure, and new diagnostic guidelines recognize conditions across the full fetal alcohol spectrum. Literature review later in this article strongly indicates that children affected by prenatal alcohol, but without the full syndrome, have diagnosable conditions that also carry a high likelihood of developmental delay and later significant problems in adaptive function. Because of this, providing early intervention services for all children diagnosed with FASD should be strongly encouraged. An even broader approach to qualifying developmentally vulnerable young children for early intervention is to classify them "at-risk"

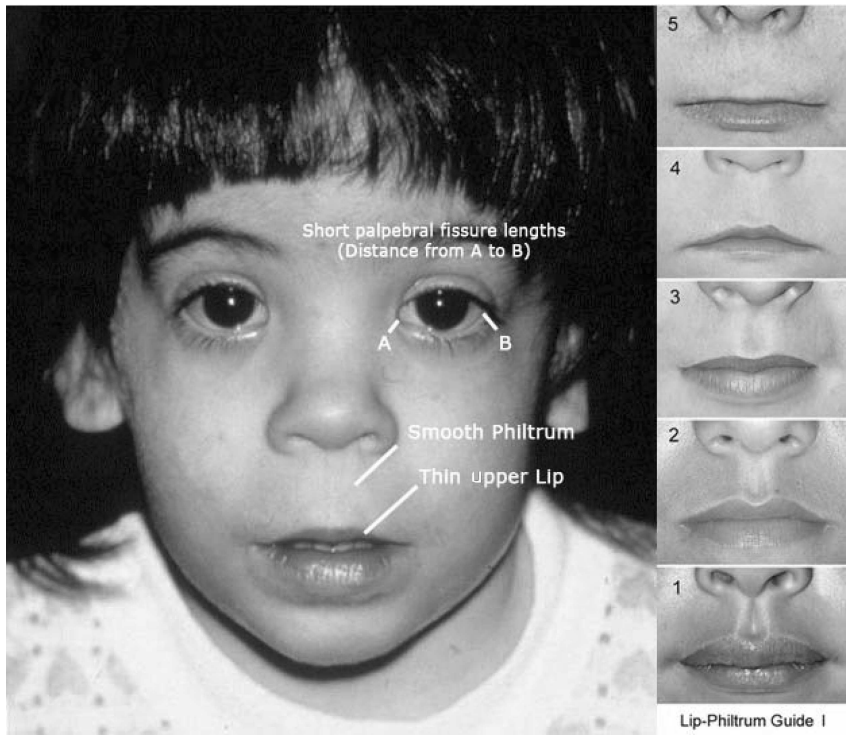

Figure 2. The 3 diagnostic facial features of fetal alcohol syndrome are as follows: (1) palpebral fissure length (eyeslit length) of 2 or more SD below the mean; (2) smooth philtrum (the vertical groove between the nose and the upper lip) (rank 4 or 5 on Lip-Philtrum Guide); (3) thin upper lip (rank 4 or 5 on Lip-Philtrum Guide). Used with permission from Susan Astley.

because of prenatal alcohol exposure coupled with evidence of emerging learning problems and/or environmental risk if this approach fits into IDEA implementation in the state where the child resides. One strategy that does *not* fit with current evidence is assuming that an alcohol-exposed child will "grow out of" apparently mild early delays, and therefore not providing services or developmental monitoring. Instead, if an exposed child does not qualify for early intervention, or improves after intervention and then no longer qualifies, a better approach lies in careful monitoring and reevaluation at key developmental transitions. This will address the possible emergence of later cognitive, language, and social difficulties.

YOUNG CHILDREN WITH PRENATAL ALCOHOL EXPOSURE AND THEIR FAMILIES

What does current scientific evidence say about young children with prenatal alcohol exposure, and what are the implications for early intervention? At present, data for young children born prenatally exposed to alcohol come from several well-designed prospective longitudinal studies of the impact of moderate or higher levels of prenatal alcohol exposure conducted in various locations in the United States, Canada, and selected other countries (with varying ethnic compositions and levels of environmental risk). There are also a few small but carefully investigated clinical

samples of young children with FASD. Just now emerging are data from larger clinical samples composed of patients seen in FASD diagnostic clinics. All these studies are the source of research findings reviewed here, given the focus of this article on the direct impact of prenatal alcohol exposure, a proven neurobehavioral teratogen, on child and family outcome. Also available in the literature are longitudinal studies of young children born polydrug-exposed, including alcohol, who typically have lives characterized by high levels of postnatal environmental risk. Findings from these latter studies are referred to briefly but not reviewed here, because these studies primarily provide insight into the impact of illicit drug exposure coupled with the larger issues of very high risk families and the impact of chemical dependency, rather than the impact of alcohol exposure before birth.

To begin, we briefly summarize new data on a large number of young children, aged birth to 8, and their families ($N = 781$), from the Washington State FAS Diagnostic and Prevention Network (FAS DPN). The FAS DPN is a statewide clinic network operating since 1993 that uses an interdisciplinary team diagnostic process and a carefully developed diagnostic system called the "4-Digit Diagnostic Code" (Astley, 2004; Astley & Clarren, 2000). The FAS DPN data discussed here come from the largest clinical database of children born prenatally alcohol-exposed believed to be in existence at this time, and includes a large number of young children. There are *no* national data on this set of neurodevelopmental disabilities, so the FAS DPN database is an excellent source of information useful to early interventionists even though conclusions are somewhat limited by geographical context. Compared to the population of Washington State, the overall FAS DPN database includes somewhat fewer females and, in terms of ethnicity, slightly underrepresents Caucasians (including those of Hispanic origin) and slightly overrepresents African Americans. Largely because of referral patterns (perhaps because of cultural differences in recognition of the problem and willingness to refer), the FAS DPN database includes somewhat more Native Americans and fewer Asians than in the larger population of Washington State. It should be noted that the FAS DPN database likely underrepresents the subset of children with FASD still living with parents grappling with chemical dependency. Research is needed on the prevalence of FASD in this high-need group.

Age of identification and important demographic characteristics

FAS DPN data show that the average age of referral for FASD diagnosis overall is $9\frac{1}{2}$ years. This means that identification of problems related to alcohol exposure often occurs rather late in children's lives. Younger children, aged birth to 8, comprise only half of those referred. Of these, the average age of identification is just more than 5, with only about a third brought in before age 4. This indicates that two thirds of younger children missed the chance for true early intervention. Improved recognition of FASD by early interventionists could bring more young children in for early diagnosis. Early diagnosis has been identified as a crucial protective factor in this population, because it is associated with more positive outcomes in adolescence and adulthood (Streissguth et al., 2004).

Many children referred for FASD diagnosis are not in the care of their birth parents. In the FAS DPN database, more than 70% of those referred for FASD diagnosis are in foster/adoptive homes. Interestingly, almost half of young children referred (and those diagnosed with FAS or Partial FAS [PFAS]) are at least third born (or later), which fits with observations that the impact of prenatal alcohol exposure may be greater for later borns. Children referred for FASD diagnosis have various racial and ethnic backgrounds. Half of those referred (and those diagnosed with FAS/PFAS) are considered Caucasian, fewer than expected given Washington State demographics, while the others come from a variety of ethnic backgrounds.

Need for referral for FASD diagnosis and advocacy by early interventionists

Surprisingly, in the FAS DPN database, very few families (4.7%) of young children are referred for FASD diagnosis from school or early intervention settings, but instead come from other referral sources such as medical, psychological, or social service providers. This low referral rate could be raised by increased awareness among early intervention providers of referral signs and the hazards of alcohol exposure, and by recognizing the importance of subtle early deficits when prenatal alcohol exposure is present (which even the children's parents may not fully appreciate).

Young children in this database receive FASD diagnoses across the whole spectrum, at rates consistent with population-based studies. This fits with wide variation in prenatal alcohol exposure seen in this population, ranging from maternal consumption of a single glass of wine once in pregnancy to daily intoxication throughout pregnancy. Of children aged birth to 8, only 7.4% receive an FAS or a PFAS diagnosis. It is this surprisingly small group who has the "face" of FAS and who is most likely to be recognized and qualify for early intervention. This is true even though their CNS dysfunction is often no more severe than that of children with ARND. A larger percentage (25.0%) of young children are diagnosed with the equivalent of "severe" ARND. While these young children are clearly in need of intervention, their families may not be able to access help without strong advocacy from early interventionists. An even larger percentage (43.4%) are diagnosed with the equivalent of "mild" ARND. These youngsters may very well show significant problems later on. Yet they are far less likely to receive any early intervention unless providers are very well informed, and have the chance to serve these children within an "at-risk" category.

Early indicators suggesting referral for an FASD diagnosis

FAS DPN data suggest that the simple presence of prenatal alcohol exposure may be the most important reason to refer for diagnosis, with higher levels of exposure especially worrisome. Behavior problems in the presence of prenatal alcohol exposure are also an important referral sign. FAS DPN data also reveal that some indicators commonly used by providers to prompt early identification of problems may *not* be as useful in signaling the need to refer for FASD diagnosis. For example, the average gestational age for children referred to FAS DPN clinics is very close to full term at 37.3 weeks. As another, very striking example, only just over half of the children show marked developmental delay in the first 3 years of life—even among those who receive an FAS/PFAS diagnosis. Indeed, more than one fourth of referred children have developmental profiles well within normal limits, with an additional third who show only mildly abnormal developmental scores. Some familiar indicators of early risk do characterize this group. Data from the FAS DPN show that most of these young children (84.5%) are also exposed to cigarettes or illicit drugs, and most (82.6%) have experienced some degree of postnatal environmental risk.

FAS DPN data reveal that some important early signs for referral for FASD diagnosis that providers could use, with training, are often being missed. It was surprisingly rare for young children to be referred for concerns about facial anomalies or growth. Indeed, diagnostic referral because of FAS-like facial features occurred for only about a tenth of these young children. Yet with careful diagnostic measurement about three quarters of young children referred showed at least 1 or more of the "sentinel" physical features. If early interventionists were more aware of these characteristic features, and/or if facial features were regularly screened as part of an early intervention intake process, diagnostic referral might occur more often. FAS DPN data do suggest that it remains important to pay close attention to even mild impairments of body growth and, especially, to small head size ($\geq$2 SD below the mean). Children with microcephaly show more developmental problems than the general population (Dolk, 1991), and over

two thirds of young children diagnosed with FAS/PFAS had microcephaly.

THE EFFECTS OF PRENATAL ALCOHOL EXPOSURE ON DEVELOPMENT IN YOUNG CHILDREN

An overview, including problems in sensory processing

What is known about the effects of prenatal alcohol exposure on development in young children? It is well established that heavy levels of prenatal alcohol exposure lead to neurobehavioral deficits, but the effects of lower levels of alcohol exposure are less clear (NIAAA, 2000). Neurobehavioral deficits arising from alcohol exposure are lifelong, but their impact on adaptive function emerges more clearly over time—and can likely be improved or made worse by postnatal experiences.

A good overview of clinically relevant findings is provided by a recent, careful study using FAS DPN data that compare a clinical sample of twenty-five 5- to 8-year-olds to an age-, gender-, and ethnicity-comparable group of 26 typically developing peers (Jirikowic, 2003). Children with FASD performed significantly more poorly than comparison peers across measures of IQ, adaptive behavior, academic performance, and sensory-motor development. A main contribution of this study was findings of sensory processing problems in the children with FASD, which validated and extended findings of an older nonstandardized questionnaire study (Morse, Miller, & Cermak, 1995). Using a standardized parent questionnaire coupled with direct testing, Jirikowic (2003) found clinically significant difficulties among children with FASD in tactile, auditory, and visual sensitivity, underresponsiveness to sensory information and sensation-seeking behaviors, and auditory filtering. Although as a group overall motor performance was in the low average range, specific difficulties were seen in sensory-motor tasks involving eye-hand coordination and timed responses, and on tests revealing persistent minor neurologic soft signs. Children with FASD showed generally lowered early academic performance (though still in the average range), with significantly low mathematics skills and early spelling skills. Overall adaptive level was lower than among children with typical development, but quite variable across alcohol-exposed individuals. For children with FASD, relative strengths in adaptive behavior were seen in ratings of motor function, and poorer performance in socialization and ability to follow the rules of daily living. Both teachers and caregivers also endorsed significantly more behavior problems among children with FASD than among typically developing peers. Interestingly, analysis of this carefully constructed and diagnosed sample revealed *no* differences in performance between girls and boys in the group with FASD. Gender differences have almost never been assessed in other studies.

Problems in early cognitive skills and learning, and sleep

Although there is a wide variety in the type and extent of deficits, problems in cognition, learning and memory, attention, and academic achievement have consistently been found among preschool (eg, Janzen, Nanson, & Block, 1995; Jirikowic, 2003) and older children with FASD (eg, Coles et al., 1997; Howell, Lynch, Platzman, Smith, & Coles, 2006; Mattson & Riley, 1998). In clinical samples with FASD, there are consistent findings of deficits in attention, wide-ranging difficulties in higher order cognitive processes called "executive functions," visual-spatial processing deficits and other problems in information processing speed and efficiency, and difficulties with mathematical problem-solving and achievement (NIAAA, 2000). Also of special interest are newer findings of alcohol effects on basic conditioned learning and other cognitive functions that reveal an impact on specific brain regions (such as the cerebellum) (eg, Jacobson et al., 2005). An interesting emerging area is potential alcohol effects on sleep, with likely sleep difficulties in respiratory control and/or circadian rhythms related to problems in brain development, and also to physical problems in midface development

leading to possible breathing obstruction (M. Chen, personal communication, January 3, 2006).

Prenatal alcohol exposure has been associated with cognitive and learning difficulties into adolescence (eg, Goldschmidt, Richardson, Cornelius, & Day, 2004; Streissguth, Barr, Sampson, & Bookstein, 1994) and beyond, though not all longitudinal studies find effects (Greene et al., 1991). Prenatal alcohol has been associated with mildly decreased performance on the Bayley Mental Scale in infancy (eg, Jacobson et al., 1993) and with mildly lowered IQ scores in preschoolers (eg, Streissguth, Barr, Sampson, Darby, & Martin, 1989). Newer longitudinal research with wider ethnic diversity and somewhat more highly exposed samples (using more sensitive measures) has found an association between alcohol exposure and early, specific cognitive and achievement difficulties. For example, infants prenatally exposed to alcohol have shown deficits in information processing and efficiency (Jacobson, Jacobson, & Sokol, 1994). These persist into the early elementary years, with additional findings of a distinctive prenatal alcohol effect on number processing (Burden, Jacobson, & Jacobson, 2005).

Deficits in speech, language, and communication

A variety of speech, language, and communication problems have been described for clinical samples of school-aged children with heavy prenatal alcohol exposure, including delays in speech acquisition, impaired receptive and expressive language, and problems in speech production (Church & Kaltenbach, 1997). Some school-aged children with FASD show discrepancies between relatively better verbal abilities (eg, vocabulary, basic syntax), and diminished capacity to use these skills effectively in social communication (which is an important foundation for developing social relationships and exchanging information) (Coggins, Friet, & Morgan, 1998). There has so far been limited clinical or longitudinal study of language and communication in infants and young children with prenatal alcohol exposure, although this is an area of intense research interest. Current clinical thinking is that young children with FASD can often acquire basic linguistic skills in a typical manner, but have difficulty becoming socially competent communicators later on and, as they grow older, show deficits in higher order language skills. These include difficulties in the more complex syntax, metacognitive abilities, and narrative skills that are tied to their cognitive difficulties in executive functions (eg, Coggins, Olswang, Carmichael Olson, & Timler, 2003).

Problems in motor development and neurologic soft signs

Alcohol-exposed individuals consistently show impairments in the development of motor control (NIAAA, 2000). In infancy, clinical studies reveal motor delays occurring more often and/or with increased severity in the presence of heavy alcohol exposure (eg, Autti-Ramo & Granstrom, 1991). Among younger children with FASD, delays in motor skills are generally mild to moderate in extent, and poor movement quality (decreased speed, efficiency, and control; abnormal balance) is often seen (eg, Osborn, Harris, & Weinberg, 1993). Significant deficits in visual-motor development (but not in motor-free visual perception), and in fine motor coordination, have been described in samples of younger children with FAS in comparison to that of typically developing peers (Adnams et al., 2001; Janzen et al., 1995).

Some longitudinal researchers have found no discernable impact of more moderate levels of social drinking on motor development in infancy (eg, Richardson, Day, & Goldschmidt, 1995) or early childhood (eg, Chandler, Richardson, Gallagher, & Day, 1996; Fried & Watkinson, 1990; Larrouque & Kaminski, 1998). Other long-term studies have found clinically significant effects, but only among infants at high exposure levels—with qualitative differences in motor behaviors (eg, deficits in imitating movements, standing, and walking) noted in infants

with lower exposure levels when compared to those with no exposure (Jacobson et al., 1993). In early childhood, longitudinal research has identified increased levels of minor neurologic soft signs among alcohol-exposed preschoolers (Larrouque et al., 1995), and a positive association between greater alcohol exposure and increased deficits in fine motor steadiness and balance (Barr, Streissguth, Darby, & Sampson, 1990).

Difficulties in adaptive behavior and social-emotional development

Difficult behaviors and social skill deficits that persist across time are an overarching concern among individuals of all ages with prenatal alcohol exposure in both clinical and longitudinal samples (eg, Olson et al., 1997; Olson, Feldman, Streissguth, Sampson, & Bookstein, 1998a; Spohr & Steinhausen, 1996). Mental health problems have been reported for a very large majority of individuals with FASD in natural history research (Streissguth, Barr, Kogan, & Bookstein, 1996), and elevated rates of psychiatric disorders are a concern (eg, Fryer, McGee, Matt, Riley, & Mattson, 2005; Murray, Olson, & Montague, 2005; O'Connor, Kogan, & Findlay, 2002a). For school-aged children with FASD, studies using questionnaires and child behavior checklists often show clinically elevated attention, social, and sometimes internalizing problems (eg, Mattson & Riley, 2000; Roebuck & Riley, 1999), and sometimes also problems with externalizing behavior and aggression (eg, Olson, Brooks, Davis, & Astley, 2004). Adaptive behavior and social skills among pre–school-aged and young school-aged children with FASD are reported as lower than expected for age and intellectual level (Mattson, Lee, Hayden, & Riley, 2005; Thomas, Kelly, Mattson, & Riley, 1998). It appears that children exposed to alcohol show relatively greater deficits in adaptive function than do clinic-referred peers after the age of 8 (Whaley et al., 2001). Clinical studies of children with FASD use terms such as impulsive, distractible, and "always on the go" to describe behavior in the preschool and elementary years (Janzen et al., 1995). In addition, while younger children with FASD have been described as engaging, verbal, apparently alert, and "bright-eyed" (Streissguth, 1997), and appear more functional than they actually are, they seem to lack social boundaries (Olson, 1994). There is wide variability in the level of these deficits, ranging from subtle to severe.

Longitudinal studies focused on infancy report early problems in behavioral regulation associated with prenatal alcohol exposure, including mild to moderate irritability, poor habituation, sleep problems, and feeding difficulties (Eyler & Behnke, 1999; Streissguth, Barr, Martin, & Herman, 1980). Among preschoolers, limited longitudinal data suggest that prenatal alcohol exposure has been associated with functional compromise that includes mild to moderate inattention and hyperactivity, and subtle to moderate impulsivity, and behavior problems (eg, Streissguth, Bookstein, Sampson, & Barr, 1993, 1995).

Developmental systems thinking adds to our understanding of the direct "main" effects of alcohol on child outcome, to better explain the reverberating impact of prenatal alcohol exposure and maternal drinking on social-emotional development across infancy and early childhood. O'Connor and her colleagues (eg, O'Connor et al., 2002b) described a transactional process in which alcohol-exposed infants show increased negative affect, their mothers have difficulty responding to these babies (perhaps because of their own depression that may be associated with a tendency to drink, and/or because of difficulties presented by the child), attachment security is compromised, and these alcohol-exposed children grow into preschoolers who show increased levels of depression at around 4 to 5 years of age. This has been shown in middle-income families, and even more clearly in low-income families who have additional risk factors that increase severity of this negative cycle. Additional analyses of middle-income families through age 6 revealed this process as most important for girls, but also found

separate trends or significant direct effects of prenatal alcohol exposure on outcome in both boys and girls (O'Connor, 2001). Further research taking a developmental systems approach, and examining issues such as gender and socioeconomic differences, is crucial to creating targeted, empirically based early intervention for children who are alcohol-exposed or have FASD diagnoses.

Cumulative risk and FASD

The impact of prenatal alcohol exposure is often coupled with that of other prenatal drug exposures, poor prenatal care, and life with parents who struggle with chemical dependency. Children may live in environments with health and safety concerns, relationship problems, and chaotic lifestyles. Longitudinal studies (eg, Arendt et al., 2004; Butz, Pulsifer, Leppert, Rimrodt, & Belcher, 2003; Singer et al., 2004) have tracked the often negative developmental outcomes of children with prenatal substance exposures in these high-risk situations. Clinical studies have examined the difficult lives of children and the potential impact of intensive interventions through comprehensive chemical dependency treatment programs serving women with children (eg, Division of Alcohol & Substance Abuse, 1999), long-term and very intensive family support programs for the highest risk mothers (eg, Grant, Ernst, Streissguth, & Stark, 2005), and intensive early intervention with family support (eg, Butz et al., 2001; Nair, Schuler, Black, Kettinger, & Harrington, 2003; Schuler, Nair, & Kettinger, 2003). These studies are sharp reminders that children with FASD may often spend at least some of their early years in an environment of cumulative risk. A developmental systems approach emphasizes that cumulative risk could be especially harmful for a child made biologically vulnerable by prenatal alcohol exposure. With the implementation of CAPTA amendments and the IDEA Improvement Act of 2004, early intervention providers will more often be linked with the child welfare system and see children who not only experience cumulative risk but also have prenatal exposures. As a result, the need to refer children for FASD diagnosis or to refer those children who are diagnosed for appropriate supplementary services will increase—and specialized training and systematic linkages with service systems that work specifically with these families will be needed.

TAKING ON THE CHALLENGE OF FASD IN EARLY INTERVENTION

A developmental systems model and its usefulness in guiding practice and research

Developmental systems thinking can guide practice for young children with FASD or with prenatal alcohol exposure, and makes clear why early intervention for this population is especially important. A useful developmental systems model was created for early intervention with children who have special needs (Guralnick, 2001). Applying this model to FASD, prenatal alcohol exposure can be seen as placing a child at risk for (or creating) biological vulnerability and "disabling child characteristics," such as sensory sensitivities or unusual learning deficits. Such deficits are individually variable and arise in multiple domains of development (perhaps in subtle ways), and may emerge more clearly or become more debilitating over time, and these child deficits (and compensatory strengths) must be comprehensively assessed.

Disabling child characteristics can disrupt existing family interaction patterns, creating information and resource needs for parents, threats to parenting confidence, and both caregiver and family stress. Comprehensive assessment of these "environmental risk factors," and risks uniquely important in this population, are also essential. One unique risk factor identified through clinical experience centers around inappropriate caregiver reactions to deficits of the child with FASD—deficits caregivers may not easily recognize as a result of alcohol-induced CNS dysfunction, but see as willful disobedience. Other pivotal family risk factors have been documented in natural history research. For this population,

past or current parental substance use, and poor quality of attachment security or poor quality of the childhood caregiving environment, is significantly associated with poor life outcomes (Streissguth et al., 2004). Protective factors hypothesized as important to this target population, such as the parent's level of optimism and parenting efficacy, use of specialized parenting practices, advocacy skill, and knowledge of FASD, or appropriate linkage to community resources (Olson et al., 2005), must also be assessed.

Early intervention should then aim to concurrently reduce the impact of disabling child characteristics and cumulative environmental risk, while at the same time enhancing protective factors. For the diagnosed child, a comprehensive intervention program can be developed and implemented, providing resource, social, and information supports, and direct intervention to enhance family interaction patterns, adjusted to the family's unique needs and targeted to the disability. For example, if a child with FASD has sensory sensitivities and processing speed deficits arising from prenatal alcohol exposure, then environmental modification and supportive OT services, caregiver education, and advocacy for later special education, might be necessary. Home visiting or clinical services to help caregivers understand alcohol-related brain damage, modify attitudes, learn specialized parenting skills, and learn effective advocacy to access existing community supports may be required when children with FASD have especially difficult behavior problems. Intervention models for such services have been developed and show promising findings in systematic research with somewhat older children with FASD (eg, Olson et al., 2005). For "at-risk" young children with prenatal alcohol exposure who may or may not yet show clinically concerning behaviors, preventative interventions are needed. For example, if attachment security is compromised in a very young child, intervention focused on enhancing secure attachment may be helpful—but may have to be adjusted for a biologically vulnerable child and the family structure (eg, foster, birth) in which the child is being raised. Early intervention models are being developed that incorporate a variety of child- and family-focused intervention strategies as needed (eg, Coles, Kable, Dent, & Lee, 2003; Gurwitch, Mulvihill, & Chaffin, 2003).

Of course, research on FASD prevention and on biological methods to ameliorate the impact of prenatal alcohol exposure on child development (such as nutritional supplements) is important. But many children are born exposed to, and affected by, prenatal alcohol, so intervention research is essential. Developmental systems thinking can also guide intervention research. Specific "disabling child characteristics" of children with FASD (or prenatal alcohol exposure) must be identified. For deficits amenable to change, targeted intervention strategies must be studied. For example, young children with FASD or prenatal exposure likely have behavior regulation problems, and targeted interventions might involve teaching caregivers specialized techniques to calm their alcohol-exposed child or help the child self-sooth. It is also imperative to conduct research on the effectiveness of more comprehensive early intervention services. These reduce "environmental risk factors" that have already been identified and increase hypothesized protective parenting and family factors. Such research is already under way through, for example, collaborative research by several research groups funded by the Centers for Disease Control and Prevention (eg, Bertrand, Sidhu, & Floyd, 2003).

Educating early intervention professionals about FASD and improving service delivery

To best serve children with FASD or prenatal substance exposure, what training is recommended for all early intervention professionals? As a start, this article presents important information about the disability. But there are additional needs for specialized preservice education and continuing education in the field, with training recommendations presented in Table 2. Training

Table 2. Suggested training topics for early intervention providers working with children affected by parental substance abuse, including alcohol*,†

How to ask questions about prenatal exposure
The process of addiction and recovery; harm reduction and relapse prevention
How to provide FASD prevention information
How to recognize and screen for the characteristic facial features of FAS, small head size, and mild or greater growth impairment
Key behavioral symptoms signaling need for diagnostic referral when in the presence of alcohol exposure
Advocacy skills to help children at risk continue to be monitored or qualify for services even with subtle deficits, and to promote services in the next intervention setting
Neurodevelopmental disabilities, and specifics about FASD; how brain development and function are affected by prenatal alcohol exposure
How to provide appropriate early intervention given current data on FASD, with a focus on environmental modification and antecedent-based positive behavior support planning
The family experience of raising children with FASD, and differences between different family structures
How parental substance abuse affects children's lives
CAPTA and IDEA regulations, and interagency efforts to improve services for children affected by parental substance abuse
Systems of care for chemical dependency treatment, FASD diagnosis, child welfare, crisis placement, foster care, adoption, adult corrections, and adult developmental disabilities service.

*Contact Drs Carmichael Olson and Jirikowic for more information on training program.
†FASD indicates fetal alcohol spectrum disorders; FAS, fetal alcohol syndrome; CAPTA, Child Abuse Prevention and Treatment Act; and IDEA, Individuals with Disabilities Education Act.

is an essential foundation to help providers develop skills to screen for FASD, guide families in obtaining a diagnosis, and effectively support the children with a diagnosis and their caregivers. Such training programs are under development and continuing education about some of these topics already exists. Beyond training, early intervention providers can build working relationships and formal connections with service provider systems that specialize in this area, such as woman-oriented chemical dependency treatment centers, FASD diagnostic clinics, FASD intervention programs, FASD parent support/advocacy organizations, and the child welfare system. At the state and local levels, interagency efforts can set up methods to raise awareness and train providers, facilitate smooth diagnostic and service referrals, modify categorical service requirements as needed, enhance collaborative care, and strengthen supports for these children and families.

Screening for FASD

Using a developmental systems approach, screening is an essential first step to identify children who should be referred for FASD diagnosis as young as possible. Screening should take place in all early intervention settings. The most efficient and effective screening method for FAS is to look for the characteristic facial features. Inexpensive and user-friendly tools are available (Lip-Philtrum Guides and FAS Facial Photographic Analysis Software) and have been used to effectively screen high-risk populations for FAS such as children in foster care (Astley, Stachowiak, Clarren, & Clausen, 2002). Screening for ARND requires effective and appropriate inquiry about prenatal alcohol exposure because, unlike the FAS facial features, there

is no pattern or type of CNS dysfunction that is specific to prenatal alcohol exposure and can clearly identify ARND. Providers should obtain training on how to ask about women's drinking and drug use, know their own agency guidelines before talking with caregivers about prenatal exposures, and remember that alcohol use at times other than pregnancy can suggest only the possibility of gestational alcohol exposure. Providers should also screen for behavior problems and growth impairment that occur in the presence of alcohol exposure.

Helping families obtain an FASD diagnostic workup

Early interventionists are well-placed to help families find a diagnostic center and obtain a workup for an identified child. Diagnostic services are most likely to be available in child guidance or child development centers, hospitals specializing in children's services, or the growing number of specialized FASD diagnostic clinics. The Substance Abuse and Mental Health Services Administration, a governmental agency, through its FASD Center for Excellence, has sponsored a Web site that as of 2007 collates all available information on diagnostic services, intervention, prevention efforts, screening programs, and research literature: http://fascenter.samhsa.gov/about/index.cfm.

Understanding and supporting families through FASD diagnosis

Early interventionists can play a key role in helping families adjust to the possibility that a child may have (or does have) FASD. Caregivers raising a child with FASD and behavior problems almost all experience high levels of child-related parenting stress (Olson et al., 2004). Perhaps more than with other neurodevelopmental disabilities, FASD carries with it an emotional overlay, because it is a birth defect that could have been prevented—and the disruptive influence of addiction will, in some way, be part of the family history. Parents' emotional reactions to the diagnosis can range from anger, to refusal to believe or listen, to acceptance—but almost always include grief, and often a firm (but likely mistaken) conviction that all problems can be dealt with by nurturing parenting or extraordinary efforts at early intervention.

Reactions of birth parents are also influenced by whether parent(s) are currently drinking or involved in the recovery process. The emotions of guilt and shame, or the psychological defense of denial, can create barriers to problem recognition or offers of intervention. Continued drinking and/or accompanying illicit drug use can mean ineffective communication and unpredictable lives, and even raise ethical and legal dilemmas for providers. Working with birth parents requires interpersonal sensitivity, and at least some specialized training (or access to consultation with providers who understand the issues of addiction and recovery). But a basic precept is that meeting families where they are, with a respectful, open, nonjudgmental, and supportive stance, is the best response by providers to the feelings of families. To maintain such a stance, however, requires that an early intervention provider think through their emotional reactions to their own and others' substance use, and to the stark reality that parental alcohol use can compromise an affected child's lifelong development.

Foster families in many states often receive training on issues related to children's special needs, and even specifically about FASD. But a child's foster placement may be temporary, so early intervention providers often must support both foster parents and caregivers who may then receive the child, including birth parents in recovery. Adoption agencies now typically openly disclose to adoptive families what is known about a child's prenatal and postnatal risks and any special needs, and families may have specifically chosen to adopt a child with FASD. But because alcohol effects may reveal themselves over time, adoptive families often find themselves struggling as they realize what is really meant by a lifelong birth defect. Therefore, they

may need intensive support from early interventionists. Furthermore, kinship adoptive placements may differ quite dramatically from nonrelative adoptive placements. Children in kinship placements are living in families touched directly by addiction. A maternal grandmother raising her grandson, for instance, might also be contending with her daughter's ongoing addiction, and the grief and shame (or anger) that arises from both the ongoing addictive behavior and its consequences that impact the child.

Providing anticipatory guidance and a model for future intervention

Early interventionists individualize and set up appropriate, clear structure and routines, promoting strengths and accommodating each child's particular deficits. Early intervention settings ideally aim to provide family-centered, integrated services that are based on a developmental framework and attempt to achieve inclusion (Guralnick, 2001). Such settings are, perhaps, a model for how children with FASD would best be served even *after* the early intervention period. It is a major challenge when a child with FASD transitions out of the early intervention system to the schools, and the child and family must then deal with the expectations of more independent function and reduced access to individualized programming that come with age. Early interventionists can smooth this transition. They can be the first to grasp the real hazards of prenatal alcohol exposure, referring children for diagnosis with FASD as early as possible, alerting caregivers to the growing child's likely emerging neurobehavioral deficits and increasing struggles with relationships, connecting families with needed additional services (such as alcohol treatment for parents)—and showing the family and the child's set of care providers what intervention strategies can really work. Early intervention providers can be proactive and essential gatekeepers and guides to the future.

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Children With Fetal Alcohol Spectrum Disorders: Problem Behaviors and Sensory Processing

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KEY WORDS
- fetal alcohol spectrum disorders
- pediatrics
- prenatal alcohol exposure
- sensory integration

OBJECTIVE. This study describes the sensory-processing and behavior profiles of a clinic-referred sample of children with fetal alcohol spectrum disorders (FASD) and examines the relationship between sensory processing and behavior.

METHODS. Outcomes on the Short Sensory Profile (SSP) and Child Behavior Checklist (CBCL) for 44 children, ages 5 to 10 years, were assessed and compared using retrospective data analysis.

RESULTS. A high proportion of the children demonstrated deficits in sensory processing and problem behaviors as measured by the SSP and the CBCL. Moreover, the correlation between the SSP and CBCL total scores ($r = -.72$) was significant.

CONCLUSION. Results provide evidence that children with FASD demonstrate problem behaviors and sensory-processing impairments as reported by parents and that sensory-processing deficits co-occur with problem behaviors at a high rate in this population. This finding suggests that deficits in sensory processing may affect the ability of children with FASD to respond adaptively to their environments.

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Fetal alcohol syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy (Jones & Smith, 1973). FAS is characterized by growth deficiency, a specific cluster of minor facial anomalies, and central nervous system damage and dysfunction (Astley & Clarren, 2000). Not all children subjected to prenatal alcohol exposure have FAS. The adverse impact of prenatal alcohol exposure presents along a continuum called *fetal alcohol spectrum disorders* (*FASD;* Bertrand et al., 2004). Clinical diagnoses that fall under the umbrella of FASD include FAS, partial FAS, static encephalopathy–alcohol exposed, and neurobehavioral disorder–alcohol exposed. The teratogenic impact of alcohol on the developing brain can lead to deficiencies in cognitive functioning, attention, memory, learning, language, auditory processing, motor skills, and problem solving (Connor & Streissguth, 1996; Mattson & Riley, 1998). Secondary disabilities affecting work, school, and social functioning may also result, which may include deficits in adaptive behavior, social competence, communication, and daily living skills (Roebuck, Mattson, & Riley, 1999; Streissguth et al., 2004; Whaley, O'Connor, & Gunderson, 2001).

Although cognitive and behavioral deficits associated with FASD have been extensively reported in the literature, sensory-processing deficits have received less attention. *Sensory processing* is a general term based on Dunn's (1999) conceptual model, which hypothesizes that a continuum of interaction exists between neurological processing of sensory input and behavioral responses. Daily activities and skills are believed to be negatively affected by sensory-processing deficits (Ayres,

1979). Sensory-processing impairments have been theoretically linked to a wide range of neurobehavioral difficulties, including problems with motor coordination, language, visual–perceptual skills, behavior, attention, learning, and emotional regulation (Ayres, 1972, 1979). Some of the documented manifestations of sensory-processing deficits include hyperactivity, distractibility, social difficulties, learning difficulties, poor organizational skills, and behavioral difficulties (Ayres, 1979). These characteristics also have been consistently reported in children with FASD (Mattson, Goodman, Caine, Delis, & Riley, 1999; Mattson & Riley, 1998).

Unfortunately, little research examines the relationship between sensory-processing and behavioral impairments in children with FASD. Findings from two studies that explored sensory processing in children with prenatal alcohol exposure suggest that children with FASD do present with sensory-processing difficulties and that these deficits co-occur with other behavioral and adaptive deficits (Jirikowic, Olson, & Kartin, in press; Morse, Miller, & Cermak, 1995). Although both studies found significantly more sensory-processing problems in children with FASD compared with typically developing children, findings were considered preliminary with limitations in instrumentation, sample size, and the depth of concurrent problem behaviors examined. More investigation of the impact prenatal alcohol exposure has on a child's ability to process and respond to sensory stimuli in his or her environment and how this relates to the child's behavioral responses to the environment is an important step that may lead to more effective intervention.

Two assessments typically administered to children in the Fetal Alcohol Syndrome Diagnostic and Prevention Network (FAS DPN) at the University of Washington are the Short Sensory Profile (SSP; Dunn, 1999), which is used to measure sensory-processing impairments, and the Child Behavior Checklist (CBCL; Achenbach, 1991; Achenbach & Rescorla, 2001), which is used to measure problem behaviors. Children's total and section scores on the SSP are classified into three categories (definite difference, probable difference, and typical performance) on the basis of parent-reported sensory-processing behaviors. Similarly, parent-reported problem behaviors on the CBCL syndrome scales, internalizing scale, externalizing scale, and total problems scores are classified into three categories (clinical, borderline, and normal).

Because of the paucity of research related to sensory processing and potential association with problem behaviors in children with FASD, this study had two purposes. The first purpose was to describe the sensory-processing characteristics and problem behaviors of 5- through 10-year-old children with FASD. The second was to explore the relationship between sensory-processing deficits and problem behaviors in children with FASD by testing the following hypotheses.

1. A significant negative correlation will exist between the CBCL total score (high scores document impaired outcome) and the SSP total score (low scores document impaired outcome).

2. Children with FASD in the SSP definite or probable group will score significantly different from children with FASD in the SSP typical group on the CBCL in the following areas: two of the syndrome scales (attention problems and social problems), the total problems score, and the externalizing problem score.

3. Children with FASD in the CBCL clinical or borderline group will score significantly different than children with FASD in the CBCL normal group on the SSP total score and five of the seven section scores (i.e., tactile sensitivity, movement sensitivity, underresponsive/seeks sensation, auditory filtering, and visual/auditory sensitivity).

4. Children with FASD who have scores that fall within the categories of definite or probable differences on the SSP will be more likely to demonstrate borderline or clinical ranges on the CBCL than children who demonstrate SSP scores within the typical performance category.

Methods

Research Design

A retrospective study was conducted using data from the Washington State FAS DPN clinical database. This database contains more than 2,000 fields of exposure and outcome data on each child with prenatal alcohol exposure who received FASD diagnostic evaluations at one of the six network clinics. Approximately half of the children are seen at the University of Washington FAS DPN clinic. Although the FAS DPN database is a clinic-referred sample, the only requirement for obtaining a FASD diagnostic evaluation at a FAS DPN clinic is a confirmed prenatal alcohol exposure at any quantity, frequency, or duration.

All children in this database received an interdisciplinary FASD diagnostic evaluation (Clarren, Carmichael Olson, Clarren, & Astley, 2000) using the FASD 4-Digit Diagnostic Code developed by Astley and Clarren (1997, 2000). The four digits of the code reflect the magnitude of expression of the four key diagnostic features of FASD in the following order: (1) growth deficiency, (2) FAS facial features, (3) central nervous system damage–dysfunction, and (4) prenatal alcohol exposure. The magnitude of expression of each feature is ranked independently on a 4-point Likert scale with 1 reflecting complete absence of the FAS feature and 4

reflecting strong presence of the FAS feature. Diagnoses were updated and coded according to the 2004 version of the 4-Digit Diagnostic Code (Astley, 2004).

Data were used in this study from all children in the FAS DPN database who met the following inclusion criteria: (1) being 5 through 10 years of age at the time of diagnosis, (2) being male or female of any race or ethnicity, (3) having one of the FASD diagnoses using the 2004 FASD 4-Digit Diagnostic Code (FAS, partial FAS, static encephalopathy–alcohol exposed, or neurobehavioral disorder–alcohol exposed); and (4) having complete data available in the database for the SSP and the CBCL. The CBCL has been administered at the FAS DPN since it first opened in 1993. The SSP was not available until 1999; thus, it was not administered in the FAS DPN until 2000. Because administration of both the CBCL and the SSP was an inclusion criterion for this study, the study population was restricted to only those diagnosed since 2000 who had data for both measures.

Instruments

SSP. Sensory-processing behaviors were measured using the SSP. The SSP is a 38-item, judgment-based caregiver questionnaire that serves as a tool for identifying a child's sensory-processing behaviors; it links these behaviors with the child's functional performance in daily activities (Dunn, 1999). The SSP, a shorter version of the Sensory Profile, was developed as a screening tool to identify children with sensory difficulties more quickly and for use as a sensory-processing measure for research purposes. The SSP is a standardized behavioral checklist with normative data. A 5-point Likert scale ranging from *always* to *never* is used to record caregiver responses. Low raw scores reflect sensory-processing problems. Moreover, the SSP includes a classification system made up of three categories (normal, probable difference, and definite difference). Psychometric properties, including reliability and validity, for the SSP are generally strong (Dunn, 1999; Dunn & Brown, 1997; Dunn & Westman, 1997; Ermer & Dunn, 1998; Watling, Deitz, & White, 2001). Internal reliability of the section scores, for a sample of 117 children, ages 3 to 17, ranged from .82 to .89 (Cronbach's alphas; Dunn, 1999). Internal reliability for the total score was .96 (Cronbach's alpha; Dunn, 1999). Intercorrelations among the SSP sections scores ranged from .25 to .76 ($p < .01$; Dunn, 1999). This finding implies that the sections are measuring differing but overlapping constructs.

Achenbach CBCL. Functional behaviors were measured using the CBCL (Achenbach, 1991) for ages 4 to 18 years and the Achenbach System of Empirically Based Assessment CBCL for ages 6 to 18 years (Achenbach & Rescorla, 2001). These are standardized tools used to assess behavioral and emotional problems that have occurred during the past 6 months.

Both versions of the CBCL are questionnaires on which a caregiver rates a child's problem behaviors. The response format is 0 (*not true*), 1 (*somewhat or sometimes true*), or 2 (*very true or often true*). Scoring provides eight syndrome scales that measure behavioral and emotional problems. These scales are anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior. The eight syndrome scales are summarized into three broader scales: internalizing (anxious/depressed, withdrawn/depressed, somatic complaints), externalizing (rule-breaking behavior, aggressive behavior), and total problems score. Moreover, the CBCL includes a classification system made up of three categories (normal, borderline, and clinical ranges). High *T* scores reflect the presence of problem behaviors. Both versions of the Achenbach CBCL are based on a careful review of the literature and empirical studies. Test–retest reliabilities and the majority of the internal consistency reliabilities were adequate to excellent for both the 1991 and 2001 CBCL scales used in this study. For the 1991 CBCL scales reported in this study, using a mean Pearson *r,* test–retest reliabilities ranged from .82 to .95, and internal consistency reliabilities (coefficient alphas) for males ranged from .62 to .96 and for females ranged from .66 to .96 (Achenbach, 1991). For the 2001 CBCL scales reported in this study, using the Pearson *r,* test–retest reliabilities ranged from .82 to .94 and internal consistency reliabilities (coefficient alphas) ranged from .82 to .97 (Achenbach & Rescorla, 2001). For both versions of the CBCL (Achenbach, 1991; Achenbach & Rescorla, 2001), content validity, criterion-related validity, and construct validity were studied extensively with one of the key findings being that both of these measures discriminate significantly between children who are referred for evaluation and those who are not referred.

Data Analysis

Descriptive statistics (e.g., means, standard deviations) were used to summarize the sociodemographic profile of the study population and outcomes from the SSP and CBCL. Because the data met the assumptions for the use of parametric statistics, the Pearson *r* correlation coefficient was used to address Hypothesis 1 regarding the linear associations between sensory processing and functional behaviors, and *t* tests were used to compare mean outcomes between the two groups. The chi-square and the Fisher exact tests were used to test for significant contrasts in proportions between groups for the test classification categories. The alpha level was set at $p \leq .05$. Because of the increased risk of Type I errors with

multiple comparisons, specific hypotheses were declared a priori. The *p* values across the CBCL and SSP subtests should be interpreted with caution and regarded as exploratory.

Results

Child Demographic and Child Development Information

Forty-four children met the study's inclusion criteria. A summary of the sociodemographic and clinical profiles of the study population is presented in Table 1. The diagnostic classifications of these 44 children spanned the full continuum under the umbrella of FASD. Eighteen children reportedly had concomitant mental health or psychiatric diagnoses, including oppositional defiant disorder (n = 6), posttraumatic stress disorder (n = 5), adjustment disorder (n = 4), conduct disorder (n = 2), and bipolar disorder (n = 1). In addition, 23 children were reported to have a diagnosis of attention deficit disorder (ADD) or attention deficit/hyperactivity disorder (ADHD).

Analyses confirmed that the 44 children included in the study population were a representative subset of all 205 children (5–10 years of age) who received a FASD diagnosis at a FAS DPN clinic since 2000. They were comparable across all variables presented in Table 1. Of the 205 children in the target population, only 44 had both a CBCL and an SSP administered. The primary reason a child did not receive a CBCL or SSP was because he or she was seen at a clinic site that did not routinely administer that assessment. The CBCL and SSP are most routinely administered at the University of Washington FAS DPN clinic site.

Because the effects of multiple home placements and short time durations in foster placement or with current caregivers were factors that also could negatively affect behavioral outcomes in this sample of children, these factors were further examined in a post hoc analysis. Findings revealed no significant correlations between the number of home placements or the duration of home placements and behavioral problems.

Table 1. Child Demographic and Development Information Gathered at Time of FASD Diagnostic Evaluation

	Children With FASD	
Variables	*n*	%
Age (years, months) at time of diagnosis (*n* = 44)		
5,0 through 6,11	14	31.8
7,0 through 8,11	17	38.6
9,0 through 10,11	13	29.5
Gender (*n* = 44)		
Male	30	68.2
Female	14	31.8
Racial/ethnic background (*n* = 44)		
White	24	54.5
African American	3	6.8
Hispanic/Latino	1	2.3
Native American	4	9.1
Other (other races, mixed races)	10	22.7
Unknown	2	4.5
Diagnostic classification (*n* = 44)		
FAS	2	4.5
Partial FAS	6	13.6
Static encephalopathy–alcohol exposed	14	31.8
Neurobehavioral disorder–alcohol exposed	22	50.0
Cognition–full scale IQ standard scores from last administered test (*n* = 39)		
130 to 140	1	2.6
115 to 129	2	5.1
100 to 114	9	23.1
85 to 99	20	51.3
70 to 84	6	15.4
60 to 69	1	2.6
Primary caregiver(s) at time of diagnosis (*n* = 44)		
Birth parent	10	22.7
Biological family member (not parent)	10	22.7
Foster parent	8	18.2
Adoptive	14	31.8
Caseworker	2	4.5
Total number of home placements at time of diagnosis (*n* = 43)		
1	9	20.9
2	15	34.9
3	6	14.0
4	5	11.6
>4	8	18.6
Length of time living with current caregiver at time of diagnosis, in years (*n* = 37)		
0 to 1	13	35.1
2 to 3	5	13.5
4 to 5	7	18.9
>5	12	32.4

Note. The sample sizes vary because data were not available for all variables for all children. Summed percentages may not equal 100 because of rounding error. FASD = fetal alcohol spectrum disorders; FAS = fetal alcohol syndrome.

SSP and CBCL Profiles

The distributions of outcomes for the SSP and the Achenbach CBCL, as reported by the primary caregivers for children with FASD, are presented in Tables 2 and 3.

Correlation Between the SSP and CBCL: Hypothesis 1

A statistically significant negative correlation between SSP and CBCL total scores (r = –.72, $p \leq .05$) was found. The relationship is a negative correlation because as the SSP total score becomes lower (indicating more sensory-processing difficulties), the CBCL score becomes higher (indicating more problem behaviors).

Associations Between Clinical Categorizations of the SSP and CBCL

Hypothesis 2. As hypothesized, relative to children with SSP total scores in the typical performance range, children with SSP total scores in the definite or probable difference clinical range had significantly higher mean *T* scores for the CBCL total problems score, externalizing problem score, and

Table 2. Achenbach Child Behavior Checklist (CBCL) Distributions of *T* Scores and Classification Groups

	Children With FASD (*N* = 44)				
			Classifications		
	T Scores		Clinical	Borderline	Normal
CBCL	*M*	*SD*	*n* (%)	*n* (%)	*n* (%)
Syndrome scales					
Anxious/depressed	65.3	10.5	14 (31.8)	5 (11.4)	25 (56.8)
Withdrawn/depressed	63.9	9.9	10 (22.7)	5 (11.4)	29 (65.9)
Somatic complaints	63.2	9.6	15 (34.1)	4 (9.1)	25 (56.8)
Social problems	70.8	9.9	22 (50.0)	10 (22.7)	12 (27.3)
Thought problems	69.2	9.1	25 (56.8)	8 (18.2)	11 (25.0)
Attention problems	74.7	12.7	25 (56.8)	9 (20.5)	10 (22.7)
Rule-breaking behavior	67.7	8.4	23 (52.3)	4 (9.1)	17 (38.6)
Aggressive behaviors	72.7	11.9	23 (52.3)	9 (20.5)	12 (27.3)
Internalizing syndrome	66.9	8.6	29 (65.9)	6 (13.6)	9 (20.5)
Externalizing syndrome	70.1	9.2	33 (75.0)	4 (9.1)	7 (15.9)
Total problems score	71.9	7.5	38 (86.4)	2 (4.5)	4 (9.1)

Note. FASD = fetal alcohol spectrum disorders.

two syndrome scale scores (attention problems and social problems). In addition, significant differences were found for the syndrome scale scores of rule-breaking behavior and thought problems (Table 4).

Hypothesis 3. Relative to children with normal CBCL total scores, children with clinical or borderline CBCL total scores had significantly lower mean scores for the SSP total score, underresponsive/seeks sensation section score, and auditory filtering section score (Table 5).

Concordance Between CBCL and SSP Category Classifications: Hypothesis 4

Table 6 presents percentages of children falling into each test category. Thirty-seven of the children in this sample (84%) demonstrated deficits in both sensory processing (definite or probable) and problem behaviors (clinical or borderline) on the CBCL. Only 2 children demonstrated no problems on either measure. Children who demonstrated deficits in sensory-processing abilities appeared more likely to also demonstrate problem behaviors. Several analyses document this concordance. When the three clinical classification groups were maintained, a significant linear-by-linear trend was observed ($\chi^2[1, N = 44] = 8.8$, $p = .003$). Because of the small sample size, some cells had expected counts less than five. When the SSP categories of "definite" and "probable" and the CBCL categories of "clinical" and "borderline" were combined to overcome the small expected cell counts, a near significant association between SSP and CBCL outcomes was observed (Fisher exact test, $p = .057$).

Discussion

This study supports previous findings indicating that sensory-processing dysfunction and problem behaviors co-occur in children with FASD (Jirikowic, Olson, et al., in press; Morse et al., 1995). A high percentage of children in this sample demonstrated both problem behaviors and sensory-processing deficits as indicated by caregiver report. Children who were

Table 3. Short Sensory Profile Distributions of Raw Scores and Classification Groups

	Children With FASD (*N* = 44)				
			Classifications		
	Raw Scores		Definite	Probable	Typical
Short Sensory Profile	*M*	*SD*	*n* (%)	*n* (%)	*n* (%)
Section scores					
Tactile sensitivity	25.2	6.3	23 (52.3)	10 (22.7)	11 (25.0)
Taste/smell sensitivity	14.2	5.9	15 (34.1)	5 (11.4)	24 (54.5)
Movement sensitivity	11.7	3.5	13 (29.5)	10 (22.7)	21 (47.7)
Underresponsive/seeks sensation	17.6	6.0	37 (84.1)	2 (4.5)	5 (11.4)
Auditory filtering	15.0	5.1	37 (84.1)	2 (4.5)	5 (11.4)
Low energy/weak	23.2	6.2	19 (43.2)	6 (13.6)	19 (43.2)
Visual/auditory sensitivity	16.7	5.7	17 (38.6)	8 (18.2)	19 (43.2)
Total score	123.6	28.5	32 (72.7)	7 (15.9)	5 (11.4)

Note. FASD = fetal alcohol spectrum disorders.

Table 4. Achenbach Child Behavior Checklist (CBCL) *T* Scores for Children With FASD Falling Within the Definite or Probable Difference and Typical Classifications on the Short Sensory Profile (SSP)

	CBCL *T* Scores					
	Children With Definite or Probable Difference Total Scores on the SSP (*n* = 39)		Children With Typical Performance Total Scores on the SSP (*n* = 5)		*t*	
CBCL	*M*	*SD*	*M*	*SD*	*t*	*p* (2-tailed)
Syndrome scales						
Anxious/depressed	65.9	10.9	60.6	4.8	1.1	.30
Withdrawn/depressed	64.4	10.3	59.8	5.6	0.9	.34
Somatic complaints	64.0	9.9	57.2	2.5	2.2	.14
Social problems	72.3	9.2	59.0	7.3	9.5	<.01
Thought problems	70.6	8.2	58.6	9.1	9.2	<.01
Attention problems	77.1	11.4	56.2	4.7	16.2	<.01
Rule-breaking behavior	68.6	8.1	60.6	8.0	4.4	.04
Aggressive behaviors	73.8	11.6	64.2	12.0	3.0	.09
Internalizing syndrome	67.7	8.8	60.8	2.5	3.0	.09
Externalizing syndrome	71.3	8.2	61.2	12.6	5.9	.02
Total problems score	73.3	6.2	61.4	8.8	14.6	<.01

Note. *n* = 44. FASD = fetal alcohol spectrum disorders.

classified in clinically concerning categories on measures of sensory processing or problem behaviors also showed significant differences in specific sensory or behavioral test domains when compared with children in normal classification categories on either measure. A statistically significant correlation between SSP and CBCL total scores ($r = -.72$) was found, indicating that children with FASD who demonstrated sensory-processing deficits were more likely to demonstrate functional behavioral deficits.

The behavioral problems in children with FASD who demonstrated sensory-processing deficits were consistent with those described in previous sensory-processing literature (Ayres, 1972, 1979; Bundy, Lane, & Murray, 2002; Livingston, 1978), as well as those described in other studies on children affected by prenatal alcohol exposure (Jirikowic, Kartin, & Olson, in press; Mattson & Riley, 2000; Whaley et al., 2001). Children with FASD who demonstrated sensory-processing deficits demonstrated significantly more externalizing behavior problems and problems in the specific domains of socialization, attention, rule breaking, and thought problems. More specifically, findings parallel those of Miller, Reisman, McIntosh, and Simon (2001), who compared 46 typically developing children (ages 3 to 13 years) with 32 children with sensory modulation dysfunction (ages 3 to 9 years). They found that children with sensory modulation dysfunction, as measured by the SSP, demonstrated more thought problems, aggressive behaviors, social problems, and attention problems as measured by the CBCL.

Table 5. Short Sensory Profile (SSP) Raw Scores for Children With FASD Falling Within the Clinical or Borderline and Normal Ranges on the Achenbach Child Behavior Checklist (CBCL)

	SSP Raw Scores					
	Clinical or Borderline Ranges on the CBCL Total Score (*n* = 40)		Normal Range on the CBCL Total Score (*n* = 4)		*t*	
SSP	*M*	*SD*	*M*	*SD*	*t*	*p* (2-tailed)
Section scores						
Tactile sensitivity	24.7	6.3	30.3	3.2	3.0	.09
Taste and smell sensitivity	13.9	6.0	17.3	2.5	1.2	.28
Movement sensitivity	11.5	3.5	13.0	2.4	0.7	.42
Underresponsive–seeks sensation	16.8	5.7	25.5	3.5	9.0	<.01
Auditory filtering	14.1	4.3	24.3	3.4	20.7	<.01
Low energy–weak	22.8	6.2	27.3	5.5	1.9	.18
Visual–auditory sensitivity	16.3	5.8	20.5	3.7	2.0	.17
Total score	120.1	27.1	158.0	18.2	7.4	.01

Note. *n* = 44. FASD = fetal alcohol spectrum disorders.

Table 6. Percentages of Children Falling Into Each Test Category (*N* = 44)

	SSP Categories		
CBCL Categories	Definite	Probable	Typical
Clinical	30 (93.8%)	6 (85.7%)	2 (40.0%)
Borderline	1 (3.1%)	0 (0.0%)	1 (20.0%)
Normal	1 (3.1%)	1 (14.3%)	2 (40.0%)

Note. SSP = Short Sensory Profile; CBCL = Child Behavior Checklist.

Although aggressive behaviors were reported by Miller and colleagues (2001) in children with sensory modulation disorder, as well as by Mattson and Riley (2000) in children with prenatal alcohol exposure, in the current study, significant differences were not found for this domain. However, trends were in the hypothesized direction.

Moreover, results indicated that children with behavioral problems also demonstrated significant differences in their abilities to process sensory stimuli as measured by caregiver report. Children who had impairments in behavior also had specific difficulty processing auditory stimuli and difficulty modulating sensory input from their surroundings as indicated by more sensation-seeking behaviors or underresponsiveness to environmental stimuli. However, the hypothesis that children with impairments in behavior would also have difficulty with tactile, visual/auditory, and movement sensitivities was not supported. These findings suggest that deficits in sensory modulation and auditory processing may result in an increased prevalence of behavioral impairments because of poor adaptive behavioral responses.

Because the majority of children (84%) demonstrating impairments in behaviors also displayed sensory-processing deficits, this study supports the notion that deficits with sensory modulation interfere with the child's abilities to demonstrate adaptive behavioral responses, leading to problem behaviors or impairments in behavioral regulation (Dunn, 1999). The strong correlation between sensory-processing impairments and behavioral problems further supports this relationship. Although concordance between those in clinically concerning categories on the both the CBCL and the SSP only approached significance statistically, possibly because of small numbers in some cells resulting in a reduction of power, the trend was in the hypothesized direction.

Finally, it is of note that children in this study also had a high prevalence of reported mental health and psychiatric diagnoses. Comorbid psychiatric conditions, such as ADD and ADHD or anxiety, mood, conduct, and explosive disorders, also have been reported in previous studies of people with prenatal alcohol exposure (Brown et al., 1991; Coles, 2001; O'Malley & Nanson, 2002). Symptoms associated with prenatal alcohol exposure, sensory-processing deficits, and mental health or psychiatric disorders warrant further exploration in terms of discerning their specific or collective impact on functional behaviors. Further research is warranted to examine the possible effects of other environmental factors (e.g., abuse, neglect) that may influence the relationship between sensory-processing impairments and functional behaviors.

Clinical Implications

This study supports the idea that a link exists between deficits in sensory processing and deficits in problem behaviors in children with FASD. Therefore, occupational therapists working with children with FASD should consider addressing sensory-processing concerns, both in the evaluation process and during intervention. The possibility of decreasing problem behaviors with sensory-based interventions and environmental modifications needs to be considered when serving a child with FASD. Perhaps occupational therapists could intervene for a child with FASD by adapting environments and educating care providers and teachers on how the child's responses to sensory stimuli may negatively influence the child's behavior.

Limitations

The following potential limitations of this study should be considered. First, the study sample was drawn from a clinical population of people referred for diagnostic evaluation. Thus, participants do not necessarily represent all people with FASD. Second, the sample was small, limiting power in some of the analyses, and the possibility of a Type I error is increased for analyses involving multiple comparisons. Third, the SSP and CBCL are standardized measures based on caregiver report. Outcomes can vary depending on which caregiver completes the report.

Direction for Future Research

Further studies should explore and clarify the relationship between sensory processing and problem behaviors in children with FASD. For example, the same hypothesis could be explored using a larger, more diverse sample of children, which would allow examination of subgroups within the population of children with FASD, such as those also diagnosed with ADHD. Gaining a better understanding of the impact prenatal alcohol exposure has on a child's ability to process and respond to sensory stimuli in his or her environment and how this relates to the child's behavioral responses to the environment is an important step in understanding this population of children. With an improved understanding of sensory processing in children with FASD, early intervention and support services could be implemented to assist with problem behaviors, potentially preventing secondary disabilities.

The relationship between problem behaviors and sensory-processing deficits in children with FASD identifies a need for research focused on the effectiveness of interventions for sensory-processing dysfunction and behavioral problems. Future results may help therapists, educators, and caregivers better understand and accommodate these children within their homes, schools, and communities.

Conclusion

Results of this study support previous research that children with FASD demonstrate significant impairments in problem behaviors (Jirikowic, Kartin, et al., in press; Mattson & Riley, 2000) and sensory processing (Jirikowic, Olson, et al., in press; Morse et al., 1995), as reported by parents. Findings further strengthen the idea that deficits in sensory processing co-occur with problem behaviors at a high rate in this population. Deficits in sensory processing, which may contribute to a range of behavioral problems, may thus affect the ability of children with FASD to demonstrate adaptive responses to their environments. ▲

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NEUROPSYCHOLOGICAL AND BEHAVIORAL OUTCOMES FROM A COMPREHENSIVE MAGNETIC RESONANCE STUDY OF CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS

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ABSTRACT

Background
Clinical and research advancements in the field of fetal alcohol spectrum disorders (FASD) require accurate and valid identification of FASD clinical subgroups.

Objectives
A comprehensive neuropsychological battery, coupled with magnetic resonance imaging, (MRI), MR spectroscopy (MRS), and functional MRI (fMRI) were administered to children with fetal alcohol spectrum disorders (FASD) to determine if global and/or focal abnormalities could be identified across the spectrum, and distinguish diagnostic subclassifications within the spectrum. The neuropsychological outcomes of the comprehensive neuroimaging study are presented here.

Methods
The study groups included: 1) FAS/Partial FAS; 2) Static Encephalopathy/Alcohol Exposed (SE/AE); 3) Neurobehavioral Disorder/Alcohol Exposed (ND/AE) as diagnosed by an interdisciplinary team using the FASD 4-Digit Code; and 4) healthy peers with no prenatal alcohol. A standardized neuropsychological battery was administered to each child and their primary caregiver by a psychologist.

Results
Use of the 4-Digit Code produced three clinically and statistically distinct FASD clinical subgroups. The three subgroups (ND/AE, SE/AE and FAS/PFAS) reflected a linear continuum of increasing neuropsychological impairment and physical abnormality, representing the full continuum of FASD. Behavioral and psychiatric disorders were comparably prevalent across the three FASD groups, and significantly more prevalent than among the Controls. All three FASD subgroups had comparably high levels of prenatal alcohol exposure.

Conclusions
Although ND/AE, SE/AE, and FAS/PFAS are distinct FASD subgroups, these groups are not distinguishable solely by their neuropsychological profiles. While all children within a group shared the same *magnitude* of neuropsychological impairment, the patterns of impairment showed considerable individual variability. MRI, MRS and fMRI further distinguished these FASD subgroups.

Key Words: *Fetal alcohol spectrum disorder (FASD), magnetic resonance (MR), FASD 4-Digit Diagnostic Code, neuropsychological*

While the focus of this report is to assess the neuropsychological, behavioral, and physical features that distinguish three FASD clinical subgroups, these data are the product of a larger, recently completed magnetic resonance imaging (MRI) (submitted for publication), MR spectroscopy (MRS)[1], and functional MRI (fMRI)[2] study of children with FASD. The key objective of the neuroimaging study was to determine if brain abnormalities could be detected between clinical subgroups along the full continuum of FASD. To conduct such a study, one must be able to *establish* distinct FASD clinical subgroups, empirically *confirm* they are distinct, and specifically *describe* how they are distinct. To establish these groups, the FASD 4-Digit Diagnostic Code[2] was employed. Thus, the primary question, and focus of this report—Were three distinct FASD subgroups successfully established, and how are they distinct? The establishment of these distinct groups was integral to the design and interpretation of the separately reported MRI, MRS, and fMRI components of this study. Presented below is the clinical rationale for the larger neuroimaging study and the essential role of this neuropsychological component.

Fetal alcohol syndrome (FAS) is a permanent birth defect syndrome caused by maternal alcohol consumption during pregnancy. FAS is defined by growth deficiency, a unique cluster of minor facial anomalies, and central nervous system (CNS) dysfunction and/or structural brain abnormalities.[4] Not all individuals with prenatal alcohol exposure present with CNS abnormalities, and not all who present with CNS abnormalities have FAS. Recently, the term FASD was coined to depict the full spectrum of outcomes observed among individuals with prenatal alcohol exposure. FASD is not a medical diagnosis. Rather, medical diagnoses like FAS, Partial FAS, Static Encephalopathy/Alcohol Exposed (SE/AE), Neurobehavioral Disorder/Alcohol Exposed (ND/AE), Alcohol Related Neurodevelopmental Disorder (ARND)[3,5,6] fall under the umbrella of FASD.

The degree of brain damage among individuals with prenatal alcohol exposure may vary from microcellular and neurochemical aberrations to gross structural anomalies. Similarly, neuropsychological/behavioral dysfunction varies along the full continuum from mild developmental delay or learning disabilities to global developmental disability.

The neuropsychological/behavioral problems in this condition *stem from* the prenatal brain damage. The specificity of the FAS facial phenotype to prenatal alcohol exposure lends credence to the clinical judgment that the neuropsychological and behavioral dysfunction observed in individuals with FAS is due, at least in part, to brain damage caused by prenatal alcohol exposure.[7-9] Unfortunately without the unique facial phenotype of FAS or at least a severe or clinically obvious expression of brain damage, the neurodevelopmental disabilities of an individual with prenatal alcohol exposure often go unrecognized and inappropriately served.[10]

Many individuals with prenatal alcohol exposure exhibit cognitive difficulties and significant maladaptation that prevent them from leading productive, independent lives.[11,12] Prior literature finds that regardless of overall intellectual level, most individuals show a range of identifiable cognitive deficits—at a rate greater than that expected given their IQ.[13] Executive functioning deficits have consistently been identified.[14-17] Deficiencies in attention are often viewed as hallmark features of prenatal alcohol exposure.[18] Deficits in complex visual-spatial skills, learning and memory, and a high prevalence and wide variety of speech/language deficits have been documented.[19] Difficulties in adaptive behavior have consistently been noted [10, 20-22] and risk of increased psychiatric disorders.[12] The profile of cognitive dysfunction among these individuals is highly variable, though there are some commonalities in functional compromise among subgroups, and conceptual models of overarching deficits have been proposed.[23] However, no single behavioral phenotype specific to alcohol teratogenicity has been described. Without a specific behavioral phenotype, attributing an alcohol-exposed child's dysfunction to brain damage is often questionable at a clinical level.[9] If indisputable evidence of brain damage (e.g., alterations in neurostructure, neurometabolites, and/or neuroactivation) could be found in alcohol-exposed individuals who present with neuropsychological deficits, but no

physical features of FAS, the "disability" of these individuals would be more clearly established, and could help them qualify for needed services.

MRI, MRS, and fMRI offer non-invasive methods for in vivo assessment of neuroabnormalities. An extensive FASD MRI research literature exists.[24-27] A few FASD studies utilizing fMRI and MRS have also been published.[28-30] In general, many of these FASD neuroimaging studies have found evidence of brain alterations among individuals with full FAS, regardless of FASD diagnostic system used, but have not always found clear evidence of brain alterations among nondysmorphic FASD subgroups. The majority of FASD neuroimaging studies have enrolled study groups diagnosed or classified as FAS, Fetal Alcohol Effects (FAE), Alcohol Related Neurodevelopmental Disorders (ARND), or Prenatal Alcohol Exposed (PEA) prior to the establishment of comprehensive, case-defined FASD diagnostic guidelines that are quickly becoming best practice.[3,5,6] The specific diagnostic criteria used to establish the FASD study groups (e.g., level of growth deficiency; type, number and severity of facial anomalies; breadth and magnitude of neuropsychological deficit; type of neurostructural anomaly present), were typically not reported. Absence of rigorous diagnostic methods can lead to diagnostic misclassification and obscure distinctions between FASD subgroups. Astley and Clarren[31] and Hoyme et al[32] have both confirmed, using two large clinical datasets, that the majority of individuals diagnosed with FAS by a gestalt approach lose that diagnostic classification when more rigorous diagnostic guidelines are applied. Misclassification error impacts study validity and reduces the power of a study to detect clinically meaningful differences between FASD subgroups.[33] If specific diagnostic features that define the FASD study groups are not reported, this limits the ability to compare outcomes across studies.

The recently completed MRI (submitted for publication), MRS[1], and fMRI[2] study was designed to overcome these limitations by using a comprehensive, case-defined diagnostic system. For this study, the FASD 4-Digit Diagnostic Code was used to establish three distinct FASD clinical subgroups (FAS/PFAS, SE/AE, and ND/AE). The focus of this report is to confirm and describe how these three FASD subgroups are clinically distinct. In describing these three clinically distinct groups, their complex neuropsychological, behavioral, and psychiatric profiles are revealed. This information is integral to the design and interpretation of the separately reported MRI, MRS[1], and fMRI[2] components of this study.

METHODS

Subjects and Study Groups

The protocol was approved by the University of Washington Human Subjects Review Board. The three FASD groups were selected from among 1,200 patients previously diagnosed by an interdisciplinary team in the WA State FAS Diagnostic & Prevention Network (FAS DPN) of clinics using a practical, comprehensive diagnostic system called the FASD 4-Digit Code.[3] Briefly, the 4 digits of the FASD 4-Digit Code[3,31] reflect the magnitude of expression of the 4 key diagnostic features of FASD, in the following order:

1. growth deficiency,
2. FAS facial phenotype,
3. CNS structural/functional abnormalities, and
4. prenatal alcohol exposure (Figure 1).

The magnitude of expression of each feature is ranked independently on a 4-point Likert scale, with 1 reflecting complete absence of the FASD feature and 4 reflecting a strong "classic" presence of the FASD feature. Each Likert rank is specifically case defined. There are 256 possible 4-digit diagnostic codes, ranging from 1111 to 4444. Each 4-digit diagnostic code falls into 1 of 22 unique clinical diagnostic categories (labeled A through V). Seven of the 22 diagnostic categories (4-Digit Categories A–C and E–H) fall broadly under the designation of FASD (A. FAS/Alcohol Exposed, B. FAS/Alcohol Exposure Unknown, C. Partial FAS/Alcohol Exposed, E-F. Static Encephalopathy/Alcohol Exposed, and G-H. Neurobehavioral Disorder/Alcohol Exposed). The three FASD study groups in this neuroimaging study represent these FASD diagnostic categories. This diagnostic system is currently being used by a wide variety of diagnostic teams in the USA and other countries.

The control population for this study was selected primarily from a large cohort of children

enrolled at birth in a University of Washington study of typical development conducted through the Department of Speech and Hearing Sciences. This registry has been maintained over the years to serve as a source of healthy controls for studies throughout the University. With the enrollment of each child in the FAS/PFAS group, a child matched on age (within 6 months), gender, and race was randomly identified and invited to enroll from the eligible SE/AE, ND/AE and Control populations. The enrollment goal was 80 subjects (20 per group).

The study enrollment procedure produced a sample of 81 children of diverse ethnicity, though with 60% Caucasian (Table 1). The age range (8 to 15.9 years) included the broadest age range of children that could be administered a comparable psychometric assessment battery and be reasonably capable of participating in the MR scanning. Each of the four study groups had 16-24 subjects successfully balanced on age, gender, and race. The 61 children with FASD were highly representative of the entire clinic sample of 1,200 from which they were drawn.

The diagnostic features specific to each group were as follows:

1. *Children in Group 1* had a 4-Digit diagnosis of **FAS or Partial FAS (FAS/PFAS)** (e.g., 4-Digit Diagnostic Categories A,B,C: with Growth Ranks 1-4, Face Ranks 3-4, CNS Ranks 3 and/or 4, Alcohol Ranks 2-4) (Figure 1). Alcohol Rank 2 (unknown exposure) could only be present if the child had a diagnosis of full FAS because the Rank 4 FAS facial features are so specific to prenatal alcohol exposure.[8,34] Since the only clinical difference between FAS and PFAS in this study was the presence of growth deficiency in the former, the two groups were combined. In summary, children in Group 1 had severe cognitive/behavioral dysfunction and the FAS facial phenotype.

2. *Children in Group 2* had a 4-Digit diagnosis of **Static Encephalopathy / Alcohol Exposed (SE/AE)** (e.g., 4-Digit Diagnostic Categories E,F: with Growth Ranks 1-4, Face Ranks 1-2, CNS Ranks 3 and/or 4, Alcohol Ranks 3-4). In summary, children in Group 2 had severe cognitive/behavioral dysfunction, comparable to Group 1, but did not have the FAS facial phenotype.

3. *Children in Group 3* had a 4-Digit diagnosis of **Neurobehavioral Disorder / Alcohol Exposed (ND/AE)** (e.g. 4-Digit Diagnostic Categories G, H: with Growth Ranks 1-4, Face Ranks 1-2, CNS Rank 2, Alcohol Ranks 3-4). In summary, children in Group 3 had prenatal alcohol exposure comparable to Groups 1 and 2, but in comparison to Groups 1 and 2 had only mild to moderate cognitive/behavioral dysfunction, and did not have the FAS facial phenotype.

4. *Children in Group 4* (**Healthy Controls / No Alcohol Exposure**) were selected based on parental report that the child was healthy, had no academic concerns, and no prenatal alcohol exposure (e.g., 4-Digit Diagnostic Category V: with Growth Ranks 1-2, FAS Face Ranks (no restrictions), CNS Rank 1, Alcohol Rank 1). In summary, these were non-exposed, healthy, average to high-functioning controls.

Using the FASD terminology introduced by the Stratton et al[11], the SE/AE group most closely reflects 'severe ARND' and the ND/AE group most closely reflects 'mild ARND'.

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Neuropsychological and behavioral outcomes from a comprehensive magnetic resonance study of children with FASD

TABLE 1 Sociodemographic and 4-Digit Diagnostic Code profiles of the four study groups

Characteristic	Groups								Statistics			
	1. FAS/PFAS [AB]		2. SE/AE		3. ND/AE		4. Control		ANOVA Overall	ANOVA Post Hoc	ANOVA A Priori LT	Chi[2]
	N = 20		N = 24		N = 21		N = 16		F (p) [C]	Duncan	F (p) [D]	Chi (p)
Gender: n (%)												
female	10	(50.0)	8	(33.3)	10	(47.6)	8	(50.0)				1.7 (.63)
Age at enrollment												
years: mean (SD)	12.7	(2.4)	12.2	(2.0)	12.4	(2.3)	12.4	(2.7)	0.1 (.96)		0.1 (.79)	
Race: n (%)												
Caucasian	12	(60.0)	11	(45.8)	12	(57.1)	13	(81.3)				[E] 5.0 (.17)
African American	6	(30.0)	4	(16.7)	6	(28.6)	2	(12.6)				
Native American	2	(10.0)	7	(29.2)	2	(9.5)	0	(0.0)				
Other	0	(0.0)	2	(8.3)	1	(4.8)	1	(6.3)				
Growth												
Growth Rank: 4-Digit Code: n (%)												
1 none	10	(50.0)	15	(62.5)	13	(61.8)	15	(93.7)				[F] 10.3 (.02)
2 mild	2	(10.0)	2	(8.3)	6	(28.6)	1	(6.3)				
3 moderate	5	(25.0)	3	(12.5)	1	(4.8)	0	(0.0)				
4 severe	3	(15.0)	4	(16.7)	1	(4.8)	0	(0.0)				
Current height percentile: mean (SD)	33.5	(31.6)	40.7	(30.4)	34.7	(30.9)	60.6	(34.2)	2.7 (.05)	132,24	5.2 (.03)	
Current weight percentile: mean (SD)	51.7	(33.4)	50.4	(34.2)	46.6	(31.2)	67.6	(24.5)	1.5 (.22)		1.7 (.19)	
Face												
Face Rank: 4-Digit Code: n (%) [C]												
1 none	0	(0.0)	4	(16.7)	7	(33.3)	10	(62.5)				

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2 mild	0	(0.0)	20	(83.3)	14	(66.7)	6	(37.5)				
3 moderate [G]	4	(20.0)	0	(0.0)	0	(0.0)	0	(0.0)				
4 severe [H]	16	(80.0)	0	(0.0)	0	(0.0)	0	(0.0)				
Facial D-Score [I]: mean (SD)	1.2	(0.9)	-0.4	(0.9)	-0.8	(0.7)	-1.5	(0.9)	31.6 (.000)	1,23,4	84.4 (.000)	
Mean R and L PFL z-score: mean (SD)	-3.0	(0.8)	-2.8	(1.2)	-2.1	(1.1)	-1.7	(0.7)	6.8 (.000)	12,34	19.4 (.000)	
Philtrum ABC-Score: n (%)												
A. Ranks 1-2: deep	0	(0)	9	(37)	7	(33)	8	(50)				37 (.000)
B. Rank 3: normal	2	(105)	11	(46)	12	(57)	8	(50)				
C. Ranks 4-5: smooth	18	(90)	4	(17)	2	(10)	0	(0)				
Lip ABC-Score: n (%)												
A. Ranks 1,2: thick	0	(0)	15	(63)	13	(62)	7	(44)				52 (.000)
B. Rank 3: normal	2	(10)	7	(29)	7	(33)	7	(44)				
C. Ranks 4,5: thin	18	(90)	2	(8)	1	(5)	2	(12)				
CNS												
CNS Ranks 1-3: 4-Digit Code												
Functional impairment level: n (%)												
1. none	0	(0.0)	0	(0.0)	0	(0.0)	16	(100)				
2. moderate	0	(0.0)	[J] 3	(12.5)	21	(100)	0	(0.0)				
3. severe	20	(100)	21	(87.5)	0	(0.0)	0	(0.0)				
CNS Rank 4: 4-Digit Code												
Structural / Neurologic Abnormality Present: n (%)	13	(65.0)	6	(25.0)	0	(0.0)	0	(0.0)				[K] 31 (.000)
Current OFC percentile: mean (SD)	28.1	(36.7)	46.6	(32.5)	54.1	(17.3)	82.7	(18.1)	11.5 (.000)	1,23,4	33.6 (.000)	
Microcephaly (OFC ≤ - 2 SD): n (%)	10	(50.0)	2	(8.3)	0	(0.0)	0	(0.0)				[L] 26 (.000)
Alcohol												
Alcohol Rank: 4-Digit Code: n (%)												
1. No exposure	0	(0.0)	0	(0.0)	0	(0.0)	16	(100)				
2. Unknown exposure	[M] 1	(5.0)	0	(0.0)	0	(0.0)	0	(0.0)				
3. Confirmed exposure: Level moderate or unk.	7	(35.0)	12	(50.0)	11	(52.4)	0	(0.0)				
4 Confirmed exposure: Level high	12	(60.0)	12	(50.0)	10	(47.6)	0	(0.0)				

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Alcohol use before pregnancy												
Days/week: mean (SD), range	5.4 (1.7)	2-7	4.0 (2.2)	1-7	5.3 (2.1)	1-7	0.9 (1.0)	0-3	19.8 (.000)	123,4	31.0 (.000)	
Most drinks/occasion: mean (SD), range	23.1 (24.8)	8-78	19.8 (26.3)	2-96	12.7 (7.7)	4-24	1.7 (1.5)	0-5	3.8 (.018)	123,4	8.7 (.005)	
Alcohol use during pregnancy												
Days/week: mean (SD), range	5.5 (1.7)	3-7	3.9 (2.1)	1-7	5.3 (2.1)	1-7	0 (0)	0-0	35.9 (.000)	123,4	35.8 (.000)	
Most drinks/occasion: mean (SD), range	11.6 (7.1)	5-24	14.1 (8.9)	3-26	11.7 (7.3)	4-24	0 (0)	0-0	14.2 (.000)	123,4	17.8 (.000)	
Drank all 3 trimesters: n (valid %)	13	(77)	13	(59)	7	(50)	0	(0)				21 (.000)
Diagnosis												
4 – Digit Code [N] Code (n)	1433	(3)	1134	(3)	1123	(4)	1111	(5)				
	1434	(3)	1233	(5)	1124	(2)	1121	(5)				
	1443	(1)	1234	(5)	1223	(3)	1211	(1)				
	1444	(3)	1243	(1)	1224	(4)	1221	(4)				
	2444	(2)	1244	(1)	2124	(1)	2221	(1)				
	3343	(1)	2233	(1)	2223	(2)						
	3344	(2)	2244	(1)	2224	(3)						
	3443	(1)	3133	(1)	3223	(1)						
	3444	(1)	3233	(1)	4223	(1)						
	4343	(1)	3243	(1)								
	4432	(1)	4233	(1)								
	4444	(1)	4234	(1)								
			4243	(1)								
			4244	(1)								
Other Factors												
Current caregiver: birthparent n (%)	3	(15.0)	3	(12.5)	3	(14.2)	15	(93.8)				39 (.000)

Neuropsychological and behavioral outcomes from a comprehensive magnetic resonance study of children with FASD

Number of home placements: mean (SD)	4.7	(5.6)	4.1	(3.3)	4.1	(2.3)	1.1	(0.3)	3.6 (.017)	123,4	8.5 (.005)	
Annual household income: ≤ $50,000 USD n (%)	10	(50.0)	7	(29.2)	6	(28.6)	1	(6.3)				8 (.042)
Illicit drug use in pregnancy: n (%)	11	(55.0)	14	(58.3)	14	(66.7)	0	(0.0)				19 (.000)
Cigarette use in pregnancy: n (%)	14	(70.0)	20	(83.3)	14	(66.7)	0	(0.0)				31 (.000)

Abbreviations: Chi^2: chi-square test across the four study groups, unless otherwise specified. Duncan: The Duncan multiple comparison range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at $p < 0.05$. F: F statistic. FAS/PFAS: FAS/partial FAS. L: left. LT: ANOVA unweighted linear trend. ND/AE: Neurodevelopmental Disorder/Alcohol Exposed. OFC: occipital frontal circumference. Overall: Overall assessment of between-group means using ANOVA. p: p-value. PFL: palpebral fissure length. R: right. SD: standard deviation. SE/AE: Static Encephalopathy/Alcohol Exposed. Unk: unknown. Z-score: number of standard deviations above/below the population-based mean. $: United States dollars.

Notations: A. Six of the 20 subjects in the FAS/PFAS group had full FAS using the 4-Digit Code. Ten of the 14 PFAS had Rank 4 Faces, but received a diagnosis of PFAS because they had no growth deficiency (Growth Rank 1). B. Two subjects had agenesis (PFAS) or hypogenesis (FAS) of the corpus callosum. C. Between groups degrees of freedom = 3; within groups df = total sample size minus 4. D. Between groups linear term degrees of freedom = 1; within groups df = total sample size minus 4. E. Caucasian versus not Caucasian. F. No growth deficiency versus mild to severe growth deficiency. G. All 4 subjects with Rank 3 faces had palpebral fissure lengths more than 2 SDs below the norm. The philtrum-lip Ranks for each subject were 3-4, 3-4, 5-3, and 4-3. H. Definition of Rank 4 FAS Face: palpebral fissure lengths 2 or more SDs below the norm, and lip and philtrum are Rank 4 or 5 on Lip-Philtrum Guide [3]. I. No child had hypo-or hypertelorism that could impact the validity of the D-score. J. All 3 children with moderate functional impairment had structural evidence of brain abnormality (microcephaly). K. Chi-square for FAS/PFAS versus SE/AE (7.1, p = .008). L. Chi-square for FAS/PFAS versus SE/AE (9.6, p = .002). M. The one child with unknown prenatal alcohol exposure had full FAS. N. The 4 digits represent the rank for growth, face, brain and alcohol, in that order [3].

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Study Participation
Participation in the study involved five visits over a 4 to 6 week study period. The neuropsychological and sociodemographic data were collected during visits 1 and 2. The neuroimaging data were collected during visits 3 and 4. The outcomes of the neuropsychological assessments were shared with the caregivers on visit 5, and submitted to the child's medical record with caregiver consent.

Sociodemographic and Clinical Assessment
A comprehensive sociodemographic and health/medication history of each child was obtained by parent interview and record review. Information included birth data, growth, and all prenatal and lifetime exposures and adverse events. For subjects with FASD, most information was obtained at the time of their FASD diagnostic evaluation. The following measures of maternal alcohol consumption were collected retrospectively, with a focus on two time points (just before pregnancy and during pregnancy): a) average and maximum number of drinks per drinking occasion, b) average number of drinking days per week, c) type of alcohol consumed (beer, wine, liquor), and d) trimester(s) during which drinking occurred. Although presence or absence of prenatal alcohol exposure was reliably documented for all subjects; more detailed information such as quantity, frequency, and duration of use was only available on 53 of the 65 alcohol-exposed subjects. This is not atypical, as accurate, detailed alcohol histories are frequently unavailable on patients presenting to a FASD diagnostic clinic. All controls had a reported absence of prenatal alcohol exposure per birth mother report.

All children had a standardized digital facial photograph taken at the time of enrollment. The facial photographs were analyzed using the FAS Facial Analysis Software[35] to generate two measures of the magnitude of expression of the FAS facial phenotype: 1) the ordinal 4-Digit Code Facial Rank (1 to 4) and 2) the continuous FAS facial D-score.[7] The D-score documents the severity of the FAS facial phenotype on a continuous scale. The higher the D-score, the more FAS-like the facial features. A D-score ≥ 0.8 is equivalent to a Rank 4 FAS facial phenotype.[7]

Neuropsychological / Psychiatric Assessments
A comprehensive, standardized assessment battery was administered to each child and their primary caregiver by a psychologist masked to group assignment (Table 2). Based on an extensive review of the prior literature, the assessment battery was designed to capture the domains of potential neuropsychological deficit seen as the result of the typically diffuse brain damage arising from alcohol teratogenesis.[5,6,23,36-39]

Magnetic Resonance Evaluation
The MRI, MRS, and fMRI components of this study are reported separately.[1,2] Briefly, all scans were acquired using a General Electric 1.5 Tesla scanner in the Diagnostic Imaging Sciences Center (DISC) at the University of Washington. MRI was used to measure the size of the following structures: total brain, frontal lobe, caudate, hippocampus, putamen; corpus callosum, and cerebellar vermis.

MRS[1] was used to measure the concentrations of neurometabolites including:

1. choline, a marker of cell membrane stability and myelination,
2. N-acetyl aspartate, a neuronal or axonal marker, and
3. creatine, a marker of metabolic activity;

in three brain regions (frontal/parietal white matter, hippocampus, and an axial slice at the level of the thalamus).

fMRI[2] was used to assess neuroactivation in seven brain regions (anterior cingulate; anterior and posterior parietal lobe; and the dorsolateral prefrontal, inferior frontal, middle frontal, and precentral regions of the frontal lobe) during performance of N-back working memory tasks. A brief summary of findings from the MRI, MRS and fMRI portions of the study is presented in the Discussion section, with citations for readers interested in further detail.

TABLE 2 Assessment battery administered to the four study groups

Soft Neurological Signs
Quick Neurological Screening Test II (QNST-II) [52]
General Intellectual Function
Wechsler Intelligence Scale for Children-Third Edition (WISC-III) [54]
Academic Achievement
Wechsler Individual Achievement Test (WIAT) Basic Reading subtest [54]
KeyMath Revised/NU: A Diagnostic Inventory of Essential Mathematics [55]
Visuospatial Skills, Visual Memory, and Organization
Beery Buktenica Developmental Test of Visual-Motor Integration (VMI) [56]
Rey Complex Figure Test (RCFT) [57]
Executive Function
Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test [58]
Delis-Kaplan Executive Function System (D-KEFS) Tower Test [58]
Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference Test [58]
Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency Test: Standard Form [58]
Wisconsin Card Sorting Test: Computer Version 3 (WCST) Research Edition [59]
Verbal Memory
California Verbal Learning Test-Children's Version (CVLT-C) [60]
Attention
Integrated Visual and Auditory Continuous Performance Test (IVA CPT) [61]
Receptive and Expressive Language
Test of Language Development-Intermediate: Third Edition (TOLD-I:3) [62] • Sentence Combining subtest (subjects aged 8 to 10 years)
Test of Language Competence-Expanded Edition (TLC-1-Expanded) Level 1 [63] • Oral Expression: Recreating Speech Arts subtest (subjects aged 8 to 9 years)
Test of Language Competence-Expanded Edition (TLC-2-Expanded) Level 2 [63] • Oral Expression: Recreating Sentences subtest (subjects aged 10 to 15.9 years)
Test of Word Knowledge (TOWK) [64] • Conjunctions and Transition Words subtest (subjects aged 11 to 15.9 years)
Adaptive Behavior
Vineland Adaptive Behavior Scales (VABS) Interview Edition, Survey Form [65]
Behavior Problems and Social Competence
Child Behavior Checklist for Ages 6-18 (CBCL/6-18) [66]
Caregiver Report of Behaviors Related to Executive Function
Behavior Rating Inventory of Executive Function (BRIEF) [67]
Psychiatric Conditions
Computerized Diagnostic Interview Schedule for Children: Parent Form (C-DISC) [68]

Predicted FASD Subgroup Contrasts

The following clinical distinctions should exist between the subgroups enrolled in this study based on: 1) the use of the FASD 4-Digit Code[3] to classify each alcohol-exposed child into one of three FASD clinical subgroups (FAS/PFAS, SE/AE, and ND/AE), and 2) prior studies assessing the performance of the 4-Digit Code.[7,31]

Growth: The FAS/PFAS group should have the highest prevalence of growth deficiency.

Face: The magnitude of expression of the FAS facial phenotype should be greatest in the FAS/PFAS group, but will also increase linearly as one progresses from Controls to FAS/PFAS.

CNS: Structural Abnormality. Head circumference should be smallest in the FAS/PFAS group, but will also decrease linearly as one progresses from the Control group to the FAS/PFAS group.

CNS: Magnitude of Neuropsychological Impairment. The FAS/PFAS and SE/AE groups should be comparably impaired, and significantly more impaired than the ND/AE and Control groups. The ND/AE group should be significantly less impaired than the FAS/PFAS and SE/AE groups and significantly more impaired than the Control group.

It is important to point out that the 4-Digit Code criteria used to rank brain dysfunction (CNS Rank 1: no dysfunction; Rank 2: moderate dysfunction; Rank 3: severe dysfunction) focus strictly on *magnitude* of dysfunction, not *pattern* of dysfunction. For example, a Rank 3 classification is defined by the presence of three or more domains of brain function, two or more standard deviations below the population mean. The diagnostic criteria do not specify *which* domains of function must be impaired. It is also important to note that the diagnostic criteria for FAS/PFAS, SE/AE, and ND/AE do not specify how much prenatal alcohol exposure must be reported. This follows a basic epidemiologic tenet; exposures and outcomes should be documented independently to validly assess the relationship(s) between the two. Thus the pattern of neuropsychological dysfunction and level of prenatal alcohol exposure will vary independent of the diagnostic criteria imposed on the FASD subgroups.

Statistical Analyses

Descriptive statistics (means, SDs, proportions) were used to summarize the sociodemographic and clinical profiles of the four study groups (Tables 1, 3, 4). For comparisons between groups, chi-square was used for categorical variables and ANOVA was used for continuous variables. When ANOVA was employed, the overall f- statistic was used to test if differences existed among the four group means. When the overall f-statistic was statistically significant, the Duncan post hoc range test was used to identify which group means differed. The Duncan test makes pairwise comparisons using a stepwise procedure. Means are ordered from highest to lowest, and extreme differences are tested first. The Duncan test sets a protection level for the error rate for the collection of tests. The Duncan test identifies homogeneous subsets of means that are not different from one another. An a priori test for linear trend was included in the ANOVA to determine if performance on the neuropsychological assessments (mean standardized score) became increasingly more impaired progressing across the four study groups from Control, to ND/AE, to SE/AE, to FAS/PFAS. This trend would be anticipated based on the 4-Digit Code diagnostic criteria. Two-tailed p-values of 0.05 were used throughout the analyses. Due to multiple comparison, p-values should be interpreted accordingly.[40,41] This study had 80% power or greater to detect the following effect sizes at a two-tailed alpha level of 0.05; 1) A difference in means equal to or greater than the standard deviation of the mean difference; 2) A 35-point or greater difference in proportions between two groups.

RESULTS

The 4-Digit Code produced four clinically and statistically distinct study groups. The three FASD clinical subgroups reflect a linear continuum of increasing neuropsychological deficit and physical abnormality (e.g., growth deficiency and FAS facial features) across the full continuum of FASD (Tables 1, 3, and 4). All three FASD subgroups had comparably high levels of prenatal alcohol exposure.

Group Differences in Key FASD Diagnostic Features (growth, face, CNS, alcohol)

Growth

The prevalence and severity of growth deficiency generally increased as one advanced across the four study groups from Controls to FAS/PFAS (Table 1). Height was more impaired than weight.

Face

The FASD Facial D-Score revealed that the magnitude of the FAS facial phenotype increased linearly across the four study groups demonstrating that the FAS facial phenotype is not simply present or absent (Table 1). This was further illustrated by the Duncan post hoc group comparisons. The magnitude of expression of the FAS facial phenotype was significantly highest among the FAS/PFAS group. The magnitude of expression was significantly lower in the SE/AE and ND/AE groups relative to the FAS/PFAS group, but significantly higher than the Control group. It is also interesting to note that although the 4-Digit Code criteria for the FAS facial phenotype requires the palpebral fissure length (PFL) to be 2 or more standard deviations below the population mean, the mean PFL for the FAS/PFAS group is 3 SD's below the mean.

CNS

By design, all subjects in the control group were without evidence of central nervous system dysfunction (CNS Rank 1). However, all those in the ND/AE group had mild to moderate dysfunction (CNS Rank 2) and all subjects in the SE/AE and FAS/PFAS groups had evidence of severe CNS dysfunction / damage (CNS Ranks 3 and 4) (Table 1). Severe dysfunction (CNS Rank 3) is defined by the presence of three or more domains (e.g., cognition, executive function, language, memory, attention, etc.) of brain function, two or more standard deviations below the norm, as measured on standardized neuropsychological tests, administered and interpreted by professionals. A Rank 3 classification does NOT dictate which domains of function must be impaired. CNS Rank 4 signifies the presence of structural brain abnormalities or frank neurological abnormality as determined by a clinical neuroradiologist or neurologist. The CNS Rank 4 classifications in Table 1 reflect the Rank 4 classifications the children received at the time of their FASD diagnostic evaluation. They do not reflect the new findings from this neuroimaging study. Nineteen subjects with FASD (13 with FAS/PFAS and 6 with SE/AE) had a CNS Rank 4 classification at the time of their FASD diagnostic evaluation. These clinical abnormalities were known prior to their enrollment into the study. Of the 13 subjects with FAS/PFAS and CNS Rank 4: 11 had microcephaly, 1 had hypogenesis of the corpus callosum (HCC), and 1 had microcephaly, agenesis of the corpus callosum (ACC), and petit mal seizures. Of the 6 subjects with SE/AE and CNS Rank 4: 4 had microcephaly, 1 had a seizure disorder and 1 had an abnormal clinical MRI (heterotopias in the left temporal lobe as interpreted by a neuroradiologist).

Within our FASD participants, one subject with PFAS had agenesis of the corpus callosum (ACC) and one subject with FAS had hypogenesis of the corpus callosum (HCC). That these subjects had callosal abnormalities were known prior to study enrollment. Interestingly, these two subjects with ACC/HCC are the only documented cases of ACC/HCC in the 2,040 patients with prenatal alcohol exposure diagnosed to date at the WA State FAS DPN clinics. In a clinical database such as the FAS DPN, MRIs are typically only available when clinically indicated (e.g., evidence of neurological abnormalities). Therefore, only 204 (10%) of the 2,040 patients evaluated at the FAS DPN had a previous MRI evaluation summarized in their medical record and 76% of the 204 MRI evaluations were interpreted as normal by the patient's neuroradiologist. Although ACC/HCC has been observed in individuals with FASD[42], ACC/HCC is not specific to prenatal alcohol exposure. The prevalence of ACC among developmentally disabled populations is estimated to be 2-3 per 100.[43] Thus, a causal link between ACC/HCC and prenatal alcohol exposure in these two individuals should not be assumed; nor can it be ruled-out.

Alcohol

Of the 65 alcohol-exposed subjects, 64 had confirmed prenatal alcohol exposure and one with full FAS had an unknown exposure (Table 1). All controls had reported absence of prenatal alcohol exposure by birth mother report. More detailed information on quantity, frequency, and/or

trimester of alcohol use was available on 53 of the 65 alcohol-exposed subjects. Reported exposure ranged from 1 to 26 drinks per drinking occasion, 1 to 7 days per week, first trimester only to all three trimesters. The mean number of days per week of drinking during pregnancy (4 to 5 days), and the maximum number of drinks per drinking occasion during pregnancy (12 to 14 drinks) were statistically comparable across the three alcohol-exposed groups (Table 1). A significantly higher proportion of subjects reported drinking all three trimesters as one advanced from the Controls to ND/AE to SE/AE to FAS/PFAS.

Maternal use of illicit drugs during pregnancy was reportedly present in 45%, 58%, 67%, and 0% of the FAS/PFAS, SE/AE, ND/AE and Control groups respectively. Use of illicit drugs was not an exclusion criteria for enrollment into this study because of its very high co-occurrence with prenatal alcohol exposure. Over 70% of the Washington State FAS DPN diagnostic clinic population has documented prenatal exposure to illicit drugs. The three FASD groups were also significantly more likely than the Control group to have other risk factors, in addition to prenatal alcohol exposure, that could adversely impact their growth and development (Table 1).

Group Differences in Neuropsychological, Behavioral and Psychiatric Outcomes

Key neuropsychological, behavioral, and psychiatric outcomes across the four study groups are presented in Tables 3 and 4. Table 3 presents mean scores on each measure for each group, reported as standard scores (or scaling appropriate for the instrument; e.g., T-scores on the CVLT-C). Table 4 presents the proportion of subjects within each group who performed in the impaired range on each measure. The "impaired range" was defined as 2 or more standard deviations below the age-appropriate population mean.

Group Mean Differences

Performance did not vary significantly with age, gender, or race. Inclusion of these covariates in between-group analyses confirmed they did not modify the outcomes. Mean performance on all assessments decreased significantly and incrementally as one advanced across the four groups from Controls, to ND/AE, to SE/AE, to FAS/PFAS (Table 3). As anticipated given the diagnostic criteria, multiple comparison tests confirmed that neuropsychological performance among the FAS/PFAS and SE/AE groups was comparably impaired—but significantly more impaired than the ND/AE and Control groups. The ND/AE group was almost always significantly less impaired than the FAS/PFAS and SE/AE groups, and significantly more impaired than the Control group on most standardized neuropsychological measures administered by the psychologists. However, the ND/AE group did not show significant differences from the Control group on direct testing measures of executive function. This was true even though caregiver report on measures of adaptation, behavior problems, and behavior rating inventory of executive functioning revealed comparable impairments in the ND/AE, SE/AE and FAS/PFAS groups, in the clinically significant range, with significantly more impairment than seen in the Control group. Psychiatric disorders were comparably prevalent across the three FASD groups, and significantly more prevalent than among the Controls. ADD/ADHD occurred most frequently. In interpreting these data, it is essential to remember that the subjects with FASD had originally sought help in a diagnostic clinic, so this high prevalence of psychiatric outcomes may not fully represent the population of all children with FASD.

The healthy, non-alcohol-exposed Control subjects showed significantly better performance on most measures when compared to the three FASD study groups. The mean full scale IQ of the healthy control group (123 + 7 SD) was higher than the population-based mean of 100 $\pm$ 15 SD. This was not surprising since children with prenatal and postnatal risk factors were screened out. Other population-based MRI and FASD-MRI studies enrolling healthy controls have reported mean full scale IQs ranging from 110 to 127.[44-46] Most FASD-MRI studies do not report the IQ or neuropsychological profile of their healthy control population. Interestingly, in spite of the Control group's relatively high IQ, many of their scores in the areas of memory, executive function, language, and adaptive behavior were, on average, solidly within normal limits compared to age peers. It is also interesting to note that the ND/AE group had a mean FSIQ (99.2 + 11.3 SD)

equivalent to the population-based mean, despite multiple prenatal/postnatal risk factors and parent-reported, significant adaptive/behavioral deficits.

Prevalence of Impairment

When the data are examined by looking at the prevalence of significant impairment on the various neuropsychological measures, compared across the diagnostic groups, a somewhat different picture emerges than that seen by comparison of group means alone (Table 4). For example, typically 20% to 50% of the children with FAS/PFAS performed significantly below the population mean in any single domain of function. A comparable prevalence of impairment was observed among the children in the SE/AE group. The prevalence was markedly less in the ND/AE group and essentially absent in the Control group. Of importance, the pattern of functional impairment varied among participants, even when they were in the same FASD subgroup diagnostic classification. While there was no consistent 'profile' of neuropsychological deficits, it was interesting to note that children with prenatal alcohol exposure (including those in the ND/AE group), had the greatest percentage of participants in the clinically impaired range on the following specific scores: Rey Complex Figure Test–Copy and Delayed Recall; the IVA Response Control Quotient; and the California Verbal Learning Test -Trial 1 Immediate Recall. Children with prenatal alcohol exposure were more likely to score in the impaired range on these tasks than on many of the more common executive function measures such as DKEFS, Tower Trail Making, Verbal Fluency, and/or Sorting Test- or the Wisconsin Card Sorting test.

Most children in the FASD groups had full scale IQs within or above the borderline range (standard score > 70), but adaptive function was well below that expected for their level of IQ (Table 4). Parent data from the Behavior Rating Inventory of Executive Function (BRIEF) questionnaire reflect that parents of alcohol-exposed children on average rate their children as falling in the range of clinical concern (>2 standard deviations from the population mean) on everyday tasks requiring executive functioning, in contrast to direct testing of executive functions on which many fewer children scored in the impaired range (90% of the children with FASD fell in the impaired range based on parent report, while only 34% were in the impaired range on the direct EF measure that had the highest percentage of impaired scores (D-KEFS:Trails).

TABLE 3 Neuropsychological behavioral and psychiatric outcomes across the four study groups

Functional Domain Psychological Test	Groups												Statistics		
	1. FAS/PFAS			2. SE/AE			3. ND/AE			4. Control			ANOVA		
	N = 20			N = 24			N = 21			N = 16			Overall	Post Hoc	A Priori LT
	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	N	Mean	(SD)	F (p) [A]	Duncan [B]	F (p) [C]
Soft Neurologic Signs															
QNST-II: Total Score (raw)	20	32.4	(17.5)	24	28.5	(9.9)	21	21.7	(11.0)	16	11.8	(6.3)	10.1 (.000)	12,23,4	29.6 (.000)
General Intellectual Function															
WISC III Full Scale IQ (ss)	20	77.5	(14.4)	24	79.3	(10.5)	21	99.2	(11.3)	16	123.9	(6.5)	67.6 (.000)	12,3,4	183.4 (.000)
WISC III Verbal IQ (ss)	20	76.0	(12.1)	24	78.8	(12.5)	21	96.3	(12.5)	16	120.8	(10.1)	53.2 (.000)	12,3,4	146.2 (.000)
WISC III Performance IQ (ss)	20	82.8	(16.6)	24	82.6	(11.3)	21	103.0	(11.7)	16	122.9	(7.3)	45.0 (.000)	12,3,4	118.9 (.000)
WISC III Freedom from Distractibility (ss)	20	78.9	(17.1)	24	79.0	(10.1)	21	92.9	(11.3)	16	120.9	(12.7)	41.3 (.000)	12,3,4	106.0 (.000)
WISC III Processing Speed (ss)	20	85.1	(13.9)	24	82.9	(13.5)	21	101.0	(14.6)	16	117.1	(10.0)	26.5 (.000)	12,3,4	66.9 (.000)
Academic Achievement															
WIAT Basic Reading (ss)	20	86.5	(15.8)	24	83.8	(14.9)	21	102.4	(14.9)	16	115.8	(8.3)	20.9 (.000)	12,3,4	51.9 (.000)
KeyMath Total (ss)	20	78.3	(14.6)	24	78.7	(9.5)	21	96.7	(11.3)	16	118.4	(11.7)	51.9 (.000)	12,3,4	125.0 (.000)
Visuospatial Skills, Visual Memory, Organization															
VMI: Total (ss)	18	76.2	(12.7)	24	81.4	(9.2)	20	90.9	(11.8)	16	102.7	(12.9)	17.8 (.000)	12,3,4	51.6 (.000)
RCFT: Copy (raw) [D]	20	17.4	(7.7)	24	20.5	(7.9)	21	25.6	(7.4)	16	31.8	(4.1)	14.3 (.000)	12,3,4	42.3 (.000)
RCFT: Immediate Recall (T)	20	30.1	(10.3)	22	28.7	(10.4)	21	40.7	(10.2)	16	49.8	(13.9)	14.5 (.000)	12,3,4	37.0 (.000)
RCFT: Delayed Recall (T)	20	28.9	(9.4)	21	29.5	(9.7)	21	38.2	(11.0)	16	53.2	(11.6)	20.8 (.000)	12,3,4	55.9 (.000)
Executive Function															
D-KEFS: Trails, Number/Letter Switch Complete Time (ss)	20	5.3	(3.9)	24	5.3	(3.4)	21	9.7	(2.7)	16	12.8	(1.7)	26.1 (.000)	12,3,4	68.5 (.000)
D-KEFS: Tower, Total Achievement (scaled)	20	7.6	(2.3)	24	8.3	(2.5)	21	9.6	(2.1)	16	10.8	(2.1)	7.0 (.000)	12,23,34	20.5 (.000)
D-KEFS: Tower, Total Rule Violation (Cumulative %tile Rank)	20	20.1	(23.4)	24	28.8	(28.8)	21	68.8	(33.8)	16	85.9	(23.3)	23.9 (.000)	12,34	65.1 (.000)
D-KEFS: Color Word Inhibit /Switch Completion Time (scaled)	20	6.4	(4.0)	23	6.6	(3.5)	21	9.3	(2.5)	16	10.6	(2.1)	8.1 (.000)	12,34	21.4 (.000)

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D-KEFS: Verbal Fluency Conds1-3 % Switch Accuracy (scaled)	20	8.9	(3.6)	24	8.8	(4.0)	21	10.8	(1.5)	16	11.1	(1.3)	3.4 (.02)	12,34	7.8 (.007)
WCST: Total Errors (ss)	18	91.2	(17.0)	24	90.0	(15.7)	21	107.7	(14.2)	16	112.8	(15.7)	10.4 (.000)	12,34	24.1 (.000)
Verbal Memory															
CVLT-C: List A, Total Trials # Correct (T)	20	38.6	(13.1)	24	38.8	(9.8)	21	50.1	(11.4)	16	61.2	(6.5)	18.9 (.000)	12,3,4	50.5 (.000)
CVLT-C: List A, Trial 1, Free Recall (T)	20	-0.9	(1.1)	24	-0.9	(0.8)	21	-0.1	(1.1)	16	0.8	(1.6)	8.2 (.000)	123,4	21.7 (.000)
Attention															
IVA: Full Response Control Quotient (ss)	20	57.7	(19.4)	23	69.5	(20.9)	21	82.9	(25.1)	16	96.0	(16.8)	11.3 (.000)	12,23,34	33.7 (.000)
Receptive and Expressive Language															
TOLD-1:3: Sentence Combining: 8-10 yrs (ss)	6	7.5	(2.4)	6	5.5	(1.0)	7	11.0	(3.4)	5	16.0	(2.5)	17.9 (.000)	12,34	41.3 (.000)
TLC-1: Recreating Speech Acts: 8-9 yrs (ss)	3	6.0	(3.5)	6	5.7	(1.9)	5	10.4	(3.8)	5	12.2	(2.3)	6.4 (.000)	213,34	13.2 (.002)
TOWK: Conjunctions & Transitions: 11-15 yrs (ss)	14	4.5	(1.7)	18	5.9	(3.8)	14	8.6	(2.6)	11	13.1	(1.6)	23.2 (.000)	12,3,4	66.6 (.000)
TLC-2: Recreating Sentences: 10-15 yrs (ss)	17	4.8	(2.0)	18	4.9	(1.9)	16	7.0	(1.5)	11	10.4	(1.3)	28.4 (.000)	12,3,4	78.8 (.000)
Adaptive Behavior															
VABS: Adaptive Behav. Composite (ss)	20	59.0	(17.5)	24	55.0	(14.2)	19	65.4	(21.1)	16	95.3	(12.3)	21.1 (.000)	123,4	46.3 (.000)
VABS: Socialization (ss)	20	67.0	(18.5)	24	64.3	(17.8)	20	71.6	(22.1)	16	100.8	(13.7)	14.5 (.000)	123,4	31.4 (.000)
Behavioral Problems and Social Competence															
CBCL: Internalizing Problems (T)	20	63.9	(9.9)	24	60.6	(10.1)	21	60.2	(12.7)	16	44.6	(7.6)	11.9 (.000)	123,4	28.8 (.000)
CBCL: Externalizing Problems (T)	20	65.2	(10.6)	24	64.4	(11.8)	21	65.0	(12.1)	16	47.1	(10.4)	10.6 (.000)	123,4	20.6 (.000)
CBCL: Social Problems (T)	20	66.0	(8.8)	24	66.8	(8.6)	21	66.9	(12.7)	16	52.3	(4.6)	10.1 (.000)	123,4	17.6 (.000)
CBCL: Attention Problems (T)	20	70.8	(11.2)	24	71.5	(10.3)	21	74.0	(15.7)	16	51.2	(1.9)	15.0 (.000)	123,4	22.5 (.000)
CBCL: Total Competence (T)	20	38.4	(7.8)	24	33.7	(7.2)	21	40.5	(9.7)	16	54.3	(9.2)	19.7 (.000)	21,13,4	37.8 (.000)
Caregiver Report of Behavior Related to Executive Function															
BRIEF: General Executive Composite (T)	20	73.2	(10.7)	24	73.0	(9.2)	21	72.0	(16.9)	16	44.2	(7.0)	25.5 (.000)	123,4	51.1 (.000)
BRIEF: Behavioral Regulation Index (T)	20	73.1	(13.2)	24	70.1	(13.4)	21	68.9	(17.1)	16	43.9	(8.0)	16.9 (.000)	123,4	38.8 (.000)

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BRIEF: Metacognition Index (T)	20	70.8	(9.4)	24	72.2	(8.2)	21	71.8	(16.0)	16	44.9	(7.1)	25.8 (.000)	123,4	46.6 (.000)
Selected Psychiatric Conditions from the C-DISC	**N**	**(Valid %)**		**N**	**(Valid %)**		**N**	**(Valid %)**		**N**	**(Valid %)**		**Chi^2 (p)**		
Attention Deficit/Hyperactivity Disorder [E]	12	(63.2)		17	(70.8)		14	(66.7)		0	(0.0)		23.5 (.000)		
Oppositional Defiant Disorder [F]	9	(47.4)		14	(58.3)		11	(52.4)		2	(12.5)		9.1 (.028)		
Conduct Disorder [G]	7	(36.8)		5	(20.8)		10	(47.6)		0	(0.0)		11.7 (.008)		
Generalized Anxiety Disorder	4	(21.1)		2	(8.3)		1	(4.8)		0	(0.0)		5.6 (.14)		
Separation Anxiety Disorder	3	(15.8)		2	(8.3)		3	(14.3)		0	(0.0)		3.0 (.39)		
Obsessive Compulsive Disorder	2	(10.5)		1	(4.2)		3	(14.3)		0	(0.0)		3.3 (.34)		
Post Traumatic Stress Disorder	2	(10.5)		1	(4.2)		0	(0.0)		0	(0.0)		3.9 (.28)		
Social Phobia	2	(11.1)		1	(4.2)		2	(9.5)		0	(0.0)		2.2 (.53)		
Major Depression / Dysthymic Disorder	1	(5.3)		2	(8.3)		1	(4.8)		0	(0.0)		3.0 (.40)		
Mania / Hypomania	1	(5.3)		0	(0.0)		0	(0.0)		0	(0.0)		3.3 (.35)		
Schizophrenia	1	(5.3)		0	(0.0)		0	(0.0)		0	(0.0)		3.3 (.35)		
Panic Disorder	0	(0)		0	(0.0)		1	(4.8)		0	(0.0)		2.9 (.41)		

Abbreviations: Chi^2: chi-square test across the four study groups. BRIEF: Behavior Rating Inventory of Executive Function. CBCL: Child Behavior Checklist for Ages 6-18 (CBCL/6-18). CC: corpus callosum. C-DISC: Computerized Diagnostic Interview Schedule for Children (Parent). CV: cerebellar vermis. CVLT-C: California Verbal Learning Test-Children's Version. D-KEFS: Delis-Kaplan Executive Function System. F: F statistic. IVA: Integrated Visual and Auditory Continuous Performance Test. LT: ANOVA a priori contrast, unweighted linear trend. p: p-value. QNST-II: Quick Neurological Screening Test-2nd Edition, Severe Discrepancy >50, Moderate Discrepancy 26-50, Normal Range 1-25. Raw: raw score. RCFT: Rey Complex Figure Test. SD: standard deviation. SS: standard score. Scaled: scaled score. T: T-score. TLC-1: Test of Language Competence-Expanded Edition Level 1 for 8-9 years. TLC-2: Test of Language Competence-Expanded Edition Level 2 for 10-15 years. TOLD-1:3: Test of Language Development-Intermediate: Third Edition for 8-10 years. TOWK: Test of Word Knowledge for 11-15 years. VABS: Vineland Adaptive Behavior Scales. VMI: Beery Buktenica Developmental Test of Visual-Motor Integration. WCST: Wisconsin Card Sorting Test: Computer Version 3. WIAT: Wechsler Individual Achievement Test. WISC III: Wechsler Intelligence Scale for Children-3rd Edition.

Notations: A. Numerator degrees of freedom = 3; denominator df = total sample size minus 4. B. The Duncan multiple comparison range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at $p < 0.05$. C. Numerator degrees of freedom = 1; denominator df = total sample size minus 4. D. Chi-square test for proportion of subjects with a RCFT Copy score $\leq 5^{th}$ percentile (FAS/PFAS n =17 (85.0%); SE/AE n=21 (87.5%), ND/AE n=10 (47.6%), Control n=0 (0%)): chi-square =37.8, p = .000. E. FASD versus Control: chi square 20.6, p = .000. F FASD versus Control: chi square 9.9, p = .002. G. FASD versus Control: Fisher exact, p = .004.

TABLE 4 Proportion of subjects within each study group with neuropsychological and behavioral scores two or more standard deviations below the population mean

Functional Domain Psychological Test[A]	FAS/PFAS N = 20		SE/AE N = 24		ND/AE N = 21		Control N = 16	
	N	(valid %)	N	(valid %)	N	(valid %)	N	(valid %)
Soft Neurologic Signs								
QNST-II: Total Raw Score >= 50	4	(20.0)	1	(4.2)	0	(0.0)	0	(0.0)
General Intellectual Function								
WISC III Full Scale IQ	7	(35.0)	6	(25.0)	0	(0.0)	0	(0.0)
WISC III Verbal IQ	7	(35.0)	6	(25.0)	1	(4.8)	0	(0.0)
WISC III Performance IQ	4	(20.0)	3	(12.5)	0	(0.0)	0	(0.0)
WISC III Freedom from Distractibility	8	(40.0)	5	(20.8)	0	(0.0)	0	(0.0)
WISC III Processing Speed	3	(15.0)	6	(25.0)	0	(0.0)	0	(0.0)
Academic Achievement								
WIAT Basic Reading	1	(5.0)	5	(20.9)	1	(4.8)	0	(0.0)
KeyMath Total	4	(20.0)	3	(12.5)	0	(0.0)	0	(0.0)
Visuospatial Skills, Visual Memory, Organization								
VMI: Total	6	(33.3)	2	(8.3)	0	(0.0)	0	(0.0)
RCFT: Copy <= 5%	17	(85.0)	21	(87.5)	10	(47.6)	0	(0.0)
RCFT: Immediate Recall	10	(50.0)	14	(58.3)	3	(14.3)	2	(12.5)
RCFT: Delayed Recall	11	(55.0)	13	(54.2)	6	(28.6)	0	(0.0)
Executive Function								
D-KEFS: Trails, Number/Letter Switch Complete Time	10	(50.0)	10	(41.7)	1	(4.8)	0	(0.0)
D-KEFS: Tower, Total Achievement)	0	(0.0)	1	(4.2)	0	(0.0)	0	(0.0)
D-KEFS: Tower, Total Rule Violation	5	(25.0)	5	(20.8)	0	(0.0)	0	(0.0)
D-KEFS: Color Word Inhibit/Switch Completion Time	5	(25.0)	7	(29.2)	0	(0.0)	0	(0.0)
D-KEFS: Verbal Fluency Conds1-3 % Switch Accuracy	2	(10.0)	4	(16.7)	0	(0.0)	0	(0.0)
WCST: Total Errors	4	(20.0)	2	(8.3)	0	(0.0)	0	(0.0)
Verbal Memory								
CVLT-C: List A, Total Trials # Correct	10	(50.0)	15	(62.5)	3	(14.3)	0	(0.0)
CVLT-C: List A, Trial 1, Free Recall	5	(25.0)	3	(12.5)	1	(4.8)	0	(0.0)

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Attention								
IVA: Full Response Control Quotient	15	(75.0)	13	(54.2)	6	(28.6)	2	(12.5)
Receptive and Expressive Language								
TOLD-1:3: Sentence Combining: 8-10 yrs	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
TLC-1: Recreating Speech Acts: 8-9 yrs	0	(0.0)	1	(4.2)	0	(0.0)	0	(0.0)
TOWK: Conjunctions & Transitions: 11-15 yrs	6	(42.9)	7	(38.9)	1	(7.1)	0	(0.0)
TLC-2: Recreating Sentences: 10-15 yrs	5	(27.8)	6	(33.3)	0	(0.0)	0	(0.0)
Adaptive Behavior								
VABS: Adaptive Behav. Composite	15	(75.0)	20	(83.3)	14	(66.7)	1	(6.3)
VABS: Socialization	13	(65.0)	15	(62.5)	12	(60.0)	1	(6.3)
Behavioral Problems and Social Competence (in clinical range)								
CBCL: Internalizing Problems	12	(60.0)	11	(45.8)	8	(38.1)	0	(0.0)
CBCL: Externalizing Problems	13	(65.0)	12	(50.0)	13	(61.9)	1	(6.3)
CBCL: Social Problems	4	(20.0)	3	(12.5)	5	(23.8)	0	(0.0)
CBCL: Attention Problems	10	(50.0)	9	(37.5)	11	(52.4)	0	(0.0)
CBCL: Total Competence	8	(40.0)	16	(66.7)	9	(42.9)	0	(0.0)
Caregiver Report of Behavior Related to Executive Function								
BRIEF: General Executive Composite	17	(85.0)	22	(91.7)	16	(76.2)	0	(0.0)
BRIEF: Behavioral Regulation Index	16	(80.0)	18	(75.0)	15	(71.4)	1	(6.3)
BRIEF: Metacognition Index	18	(90.0)	23	(95.8)	16	(76.2)	0	(0.0)

Abbreviations: FAS/PFAS: fetal alcohol syndrome/partial FAS. ND/AE: neurodevelopmental disorder/alcohol exposed. SE/AE: static encephalopathy/alcohol exposed.
Notations: A. See Table 2 for definition of psychological tests.

DISCUSSION

Three clinically and statistically distinct FASD study groups were successfully established using a comprehensive diagnostic system. Use of the FASD 4-Digit Code revealed three FASD study groups (ND/AE, SE/AE and FAS/PFAS) that reflect a linear continuum of increasing neuropsychological impairment and physical abnormality (e.g., growth deficiency and FAS facial anomalies). This represents the full spectrum of FASD. Although ND/AE, SE/AE, and FAS/PFAS are distinct FASD subgroups, a central finding of this study is that they are not distinguishable solely by their neuropsychological profiles. While all children within a group shared the same *magnitude* of neuropsychological impairment, no two children necessarily shared the same *pattern* of impairment. The creation of these three distinct FASD subgroups played a vital role in the interpretation of the MRI, MRS[1], and fMRI[2] outcomes of this study. Concurrently, the MRI, MRS, and fMRI outcomes played a vital role in further confirming the three FASD subgroups were clinically distinct.

While the neuropsychological, behavioral, and psychiatric profiles of the current FASD group closely parallel those presented in the FASD literature[23,47], the FASD literature presents a somewhat mixed picture on whether significant neuropsychological differences exist between FASD subgroups with and without the physical features of FAS or between nondysmorphic FASD groups and healthy controls.[17,48,49] The current study found clear neuropsychological differences between these various groups. Most of the differences observed between FASD subgroups, however, would not have been identified if the SE/AE and ND/AE groups had been combined into one nondysmorphic FASD group (typically referred to as ARND, FAE, or PEA in other studies).

Findings from the larger neuroimaging study further confirmed the distinction between these three FASD subgroups, and the notion that children with FASD differ in important ways from healthy, non-alcohol-exposed peers. The larger neuroimaging study also served to further validate[7,8,31,34] the measurement scales and procedures for diagnostic classification used in the FASD 4-Digit Diagnostic Code. Data from the larger study revealed significant, neurostructural neurometabolite[1] and neuroactivation[2] differences between FASD diagnostic subgroups, and between nondysmorphic FASD subgroups and controls. For example MRI data from the larger study reveal that the frontal lobe was disproportionately smaller only in the FAS/PFAS group (the only group with the FAS facial phenotype as defined by the 4-Digit Code) (Figure 1B). The frontal lobe and FAS facial features share the same embryologic origin (the frontal nasal prominence.[50] The caudate was disproportionately smaller only in the FAS/PFAS and SE/AE groups (the only two groups with severe neuropsychological impairment). Neurostructural abnormalities were also observed in the ND/AE group. The prevalence of participants in the ND/AE, SE/AE and FAS/PFAS groups with one or more brain regions found to be 2 or more standard deviations below the mean size observed in the control group increased significantly and incrementally from 43% to 58% to 75%. In addition, the prevalence/severity of structural brain abnormality increased significantly as one progressed from CNS Rank 1 (no dysfunction) to Rank 2 (mild-moderate dysfunction) to Rank 3 (severe dysfunction). Indeed, when these CNS Ranks were first defined in 1997 [31] the underlying principle was that as the magnitude and breadth of functional impairment increased, the probability of underlying structural abnormality would increase. It is for this reason that the 4-Digit CNS Ranks 1, 2, and 3 were labeled “unlikely”, “possible”, and “probable” underlying CNS abnormality respectively (Figure 1A). MRS[1] data from the larger study reveal the choline concentration (a marker of cell membrane stability and myelination) in a frontal/parietal white matter region was significantly lower only in the FAS/PFAS group. Finally, fMRI[2] data reveal that neuroactivation during a difficult “2-back” working memory task decreased significantly and incrementally progressing across the four groups from Controls, to ND/AE, to SD/AE, to FAS/PFAS. These neuroimaging reports and previous studies[7,31] demonstrate that these subgroup differences would not have been identified if the SE/AE and ND/AE groups had been combined into one nondysmorphic FASD group, or if less rigorous diagnostic methods and

allowed the FAS/PFAS and SE/AE groups to be intermixed.

It is clear from the comprehensive neuroimaging study that MRI, MRS[1], and fMRI[2] can illuminate underlying brain abnormality across the full spectrum of FASD in new and important ways. What is learned about the teratogenic effects of alcohol on neurostructure, neurometabolites, and neuroactivation may help to clarify why individuals exposed to prenatal alcohol perform as they do on standardized neuropsychological measures. Certainly these neuroimaging technologies also provide convincing evidence that cognitive and behavioral deficits among those prenatally alcohol-exposed are, to an important extent, "brain-based." These physical findings validate the importance of detecting and diagnosing the medical condition (and developmental disability) of FASD so that medication and behavioral interventions can be appropriately employed

If we can improve our ability to physically identify the presence of CNS abnormality across the full spectrum of FASD, this may facilitate access to essential social and educational services for those with FASD. In truth, in the absence of definitive physical evidence of underlying organic CNS damage, it is often questioned whether individuals along the spectrum are really impacted by their prenatal exposure. As Stratton et al.[11] note in the landmark Institute of Medicine report, not all individuals with FASD meet eligibility criteria for educational, developmental disability or mental health services. This is because FAS, and especially ARND, are typically not recognized as diagnostic labels in many existing service systems. This is also because children with FASD often have neuropsychological profiles that do not make them eligible for the services they actually need. The deficit patterns of children with FASD are characterized by deficits across multiple domains, and IQ scores may not reflect their full range of deficits or extent of functional compromise. Children with FASD often do not receive test scores that are low enough to qualify for services until their later elementary school (or even middle school) years, so many do not qualify for intervention that occurs sufficiently early. Indeed, children with FASD may receive services targeting disruptive or antisocial behavior, rather than services that more appropriately address the complex cognitive and learning deficits that comprise the foundation for their behavioral difficulties and problems in adaptive function. The clinical literature suggests that these deficits have an increasingly debilitating effect as children move into the elementary school years and beyond, interfering with successful daily function.[51]

FIG. 1 A) FASD 4-Digit Diagnostic Code grid. FASD is defined by growth deficiency, specific FAS facial features, evidence of CNS damage and prenatal alcohol exposure. The 4-Digit Code ranks each of these areas on 4-point, case-defined, Likert scales. The 4-Digit Code (3444) inserted in the grid is 1 of 12 codes that meet the diagnostic criteria for FAS.[3] **B)** FASD 4-Digit Code FAS facial phenotype (view image). The Rank 4 FAS facial phenotype determined with the 4-Digit Diagnostic Code requires the presence of all 3 of the following anomalies: (1) palpebral fissure length 2 or more standard deviations below the norm; (2) smooth philtrum (Rank 4 or 5 on the Lip-Philtrum Guide), an (3) thin upper lip (Rank 4 or 5 on the Lip-Philtrum Guide). Examples of the full Rank 4 FAS facial phenotype for Caucasian, Native American, African American and Asian American children are shown.

A.

				3	**4**	**4**	**4**		
Severe	Severe	Definite	(4)		**X**	**X**	**X**	(4)	High risk
Moderate	Moderate	Probable	(3)	**X**				(3)	Some risk
Mild	Mild	Possible	(2)					(2)	Unknown
None	None	Unlikely	(1)					(1)	No Risk
	FAS			Growth	Face	CNS	Alcohol		
Growth Deficiency	**Facial Features**	**CNS Damage**							**Prenatal Alcohol**

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Magnetic Resonance Imaging Outcomes From a Comprehensive Magnetic Resonance Study of Children With Fetal Alcohol Spectrum Disorders

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Background: Magnetic resonance (MR) technology offers noninvasive methods for in vivo assessment of neuroabnormalities.

Methods: A comprehensive neuropsychological/psychiatric battery, coupled with MR imaging, (MRI), MR spectroscopy (MRS), and functional MRI (fMRI) assessments, were administered to children with fetal alcohol spectrum disorders (FASD) to determine if global and/or focal abnormalities could be identified, and distinguish diagnostic subclassifications across the spectrum. The 4 study groups included: (i) fetal alcohol syndrome (FAS)/partial FAS (PFAS); (ii) static encephalopathy/alcohol exposed (SE/AE); (iii) neurobehavioral disorder/alcohol exposed (ND/AE) as diagnosed with the FASD 4-Digit Code; and (iv) healthy peers with no prenatal alcohol exposure. Presented here are the MRI assessments that were used to compare the sizes of brain regions between the 4 groups. The neuropsychological/behavioral, MRS, and fMRI outcomes are reported separately.

Results: Progressing across the 4 study groups from Controls to ND/AE to SE/AE to FAS/PFAS, the mean absolute size of the total brain, frontal lobe, caudate, putamen, hippocampus, cerebellar vermis, and corpus callosum length decreased incrementally and significantly. The FAS/PFAS group (the only group with the 4-Digit FAS facial phenotype) had disproportionately smaller frontal lobes relative to all other groups. The FAS/PFAS and SE/AE groups [the 2 groups with the most severe central nervous system (CNS) dysfunction] had disproportionately smaller caudate regions relative to the ND/AE and Control groups. The prevalence of subjects in the FAS/PFAS, SE/AE, and ND/AE groups that had 1 or more brain regions, 2 or more SDs below the mean size observed in the Control group was 78, 58, and 43%, respectively. Significant correlations were observed between size of brain regions and level of prenatal alcohol exposure, magnitude of FAS facial phenotype, and level of CNS dysfunction.

Conclusions: Magnetic resonance imaging provided further validation that ND/AE, SE/AE, and FAS/PFAS as defined by the FASD 4-Digit Code are 3 clinically distinct and increasingly more affected diagnostic subclassifications under the umbrella of FASD. Neurostructural abnormalities are present across the spectrum. MRI could importantly augment diagnosis of conditions under the umbrella of FASD, once population-based norms for structural development of the human brain are established.

Key Words: Fetal Alcohol Spectrum Disorder, Magnetic Resonance Imaging, FASD 4-Digit Diagnostic Code.

FETAL ALCOHOL SYNDROME (FAS) is a permanent birth defect syndrome caused by maternal alcohol consumption during pregnancy. FAS is defined by growth deficiency, a unique cluster of minor facial anomalies, and central nervous system (CNS) dysfunction and/or structural brain abnormalities (Smith, 1979). The cognitive/behavioral problems in this condition stem from prenatal brain damage. Not all individuals with prenatal alcohol exposure present with measurable CNS dysfunction or structural brain abnormalities, and not all who present with measurable CNS dysfunction or structural brain abnormalities have FAS. Recently, the term fetal alcohol spectrum disorders (FASD) was coined to depict the spectrum of outcomes observed

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among individuals with prenatal alcohol exposure. The degree of brain damage among individuals with prenatal alcohol exposure may vary from microcellular and neurochemical aberrations to gross structural anomalies. Similarly, cognitive/behavioral dysfunction varies along the full continuum from mild developmental delay or learning disabilities to global developmental disability (Astley et al., 2009b). The specificity of the FAS facial phenotype to prenatal alcohol exposure lends credence to the clinical judgment that the cognitive and behavioral dysfunction observed in individuals with FAS is due, at least in part, to brain damage caused by a teratogen (Aase et al., 1995; Astley and Clarren, 2001; Astley et al., 2002). Unfortunately, without the unique facial phenotype of FAS or at least a severe or clinically obvious expression of brain damage, the neurodevelopmental disabilities of an individual affected by prenatal alcohol exposure often go unrecognized and inappropriately served (Streissguth et al., 1993).

Many individuals with prenatal alcohol exposure exhibit cognitive difficulties and significant maladaptation that prevent them from leading productive, independent lives (Stratton et al., 1996; Streissguth et al., 2004). Across the population, the profile of cognitive dysfunction among individuals with prenatal alcohol exposure is highly variable, although there are some commonalities in functional compromise among subgroups, and conceptual models of overarching deficits have been proposed (Kodituwakku, 2007). However, no single behavioral phenotype specific to alcohol teratogenicity has been described. Without a behavioral phenotype specific to the teratogen alcohol, attributing an alcohol-exposed child's dysfunction to brain damage is often questionable at a clinical level (Aase et al., 1995). If indisputable evidence of brain damage (e.g., alterations in neurostructure, neurometabolites, and/or neuroactivation) could be found in these individuals, and linked to behavioral deficit, diagnostic efforts could be improved. The "disability" of these alcohol-exposed children would be clearly established, and help facilitate eligibility for needed services. Further, if specific alterations in neurostructure, neurometabolites, and/or neuroactivation could be linked to clinically meaningful, discrete neuropsychological deficits, development of appropriate intervention programs could be accelerated.

The overall goal of this research study was to determine if magnetic resonance (MR) imaging (MRI), MR spectroscopy (MRS), and/or functional MRI (fMRI) could serve as noninvasive methods for definitively identifying global and/or focal brain abnormality across the full continuum of FASD, and distinguish diagnostic subclassifications within the spectrum. The results of this comprehensive study are presented in 4 separate reports: MRI (presented here) and the neuropsychological/behavioral (Astley et al., 2009b), MRS (Astley et al., 2009c), and fMRI (Astley et al., 2009a) outcomes reported separately. The focus on FASD diagnostic methodology in this report directly responds to the following Research Recommendations for Diagnostic Criteria published in the Institute of Medicine report on FASD (Stratton et al., 1996) research: (i) to evaluate the utility, reliability, and validity of schemes for classification and diagnosis, (ii) to identify potential structural or functional brain abnormalities and other neurobiological indices that may be associated with or distinguish FAS, alcohol-related neurodevelopmental disorder (ARND), or alcohol-related birth defect, and to relate these abnormalities and indices to cognitive and behavioral correlates.

Magnetic resonance imaging allows for very sensitive assessment of size, shape, spatial orientation, and even tissue composition of selected brain regions. Numerous FASD MRI studies have been conducted to date (Archibald et al., 2001; Bookstein et al., 2002b; Mattson et al., 2001; Miller et al., 1999; Riley et al., 1995; Sowell et al., 2001b, 2002a,b). Documented abnormalities include reduction in overall brain size, reduction in absolute size of selected brain regions (basal ganglia, caudate, cerebellum, and anterior/posterior regions of the corpus callosum), disproportionate reduction of the caudate, alterations in shape and spatial orientation of the corpus callosum, and white matter hypoplasia in the parietal and temporal lobes.

The majority of FASD MRI studies published to date have enrolled study groups diagnosed or classified as FAS, fetal alcohol effects (FAE), ARND, or prenatal exposure to alcohol (PEA) prior to the establishment of comprehensive, case-defined FASD diagnostic guidelines that are quickly becoming best practice (Astley, 2004; Bertrand et al., 2004; Chudley et al., 2005). The specific diagnostic criteria used to establish the FASD study groups (e.g., level of growth deficiency; type, number and severity of facial anomalies; breadth and magnitude of neuropsychological impairment; type of neurostructural anomaly present), providing confirmation that FASD diagnostic subgroups are clinically and statistically distinct from each other, are typically not reported. Absence of rigorous diagnostic methods can lead to diagnostic misclassification. Astley and Clarren (2000) and Hoyme and colleagues (2005) have both demonstrated that individuals diagnosed with FAS by a gestalt approach often lose that diagnostic classification when more rigorous diagnostic guidelines are applied. Misclassification impacts study validity and reduces the power of a study to detect clinically meaningful differences between FASD subgroups. If specific diagnostic features that define the FASD study groups are not clearly reported, this limits the ability to compare outcomes across studies.

In general, most FASD MRI studies have found significant differences between FAS and control groups, regardless of diagnostic system used; but have not always found differences between clinical subgroups on the fetal alcohol spectrum. In the current study, the sizes of brain regions were compared between 3 FASD diagnostic subgroups and a healthy control group with no prenatal alcohol exposure. An important goal of this MRI study was to determine if meaningful neurostructural differences do exist between FASD subgroups when the subgroups, including FAS, are rigorously case-defined (Astley, 2004) and confirmed to be clinically and statistically distinct from one another (Astley et al., 2009b).

MATERIALS AND METHODS

Subjects and Study Groups

The protocol was approved by the University of Washington Human Subjects Review Board. The goal of the study was to create 3 clinically distinct and increasingly less affected FASD study groups and 1 healthy unexposed control group that fell along the following ordinal scale: (i) significant brain damage/dysfunction with the FAS facial phenotype; (ii) significant brain damage/dysfunction without the FAS facial phenotype; (iii) mild to moderate brain dysfunction without the FAS facial phenotype, and (iv) healthy with no prenatal alcohol exposure. The 3 FASD groups were selected from among 1,200 patients previously diagnosed by an interdisciplinary team in the WA State FAS Diagnostic & Prevention Network (FAS DPN) of clinics using a practical, comprehensive diagnostic system called the FASD 4-Digit Code (Astley, 2004; Astley and Clarren, 2000). Briefly, the 4 digits of the FASD 4-Digit Code reflect the magnitude of expression of the 4 key diagnostic features of FASD, in the following order: (i) growth deficiency, (ii) characteristic FAS facial phenotype, (iii) CNS structural/functional abnormalities, and (iv) prenatal alcohol exposure (Fig. 1). The magnitude of expression of each feature was ranked independently on a 4-point Likert scale, with 1 reflecting complete absence of the FASD feature and 4 reflecting a strong "classic" presence of the FASD feature. Each Likert rank is specifically case-defined. There are 256 possible 4-digit diagnostic codes ranging from 1111 to 4444. Each 4-digit diagnostic code falls into 1 of 22 unique clinical diagnostic categories (labeled A through V). Seven of the 22 diagnostic categories (4-Digit Categories A–C and E–H) fall under the umbrella of FASD [A, FAS/alcohol exposed; B, FAS/alcohol exposure unknown; C, PFAS/alcohol exposed; E and F, static encephalopathy/alcohol exposed (SE/AE); and G and H, neurobehavioral disorder/alcohol exposed (ND/AE)]. The 3 FASD study groups in the current study represent these FASD diagnostic categories. This diagnostic system is currently being used

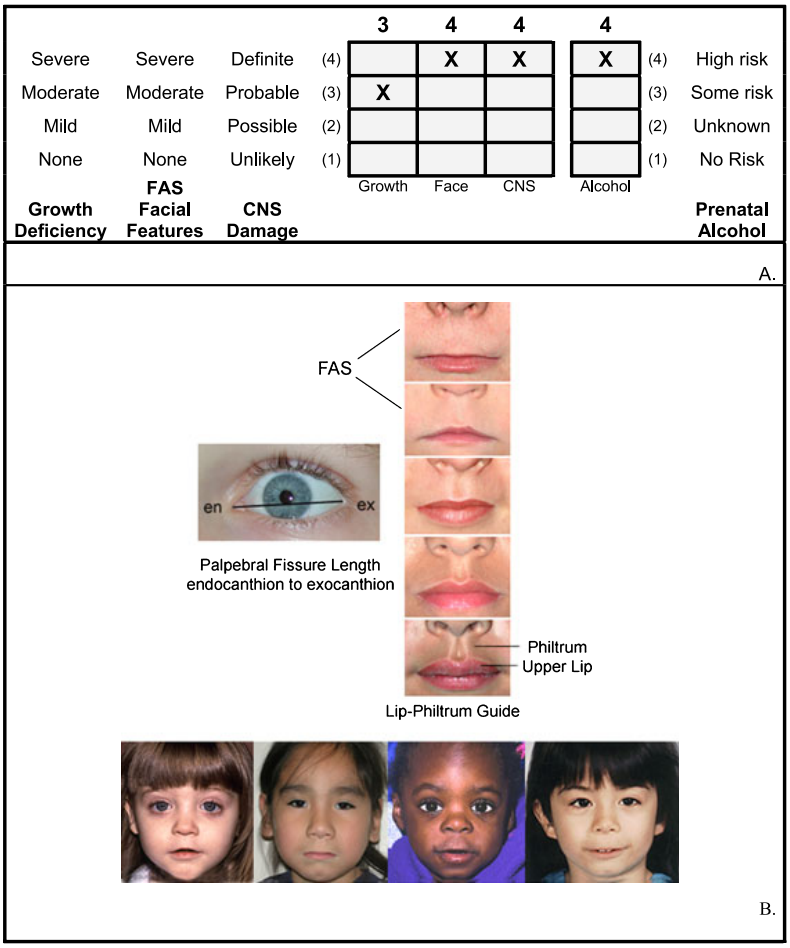

Fig. 1. (**A**) FASD 4-Digit Diagnostic Code grid. FASD is defined by growth deficiency, specific FAS facial features, evidence of CNS damage and prenatal alcohol exposure. The 4-Digit Code ranks each of these areas on 4-point, case-defined Likert scales. The 4-Digit Code (3444) inserted in the grid is 1 of 12 codes that meet the diagnostic criteria for FAS (Astley, 2004). (**B**) FASD 4-Digit Code FAS facial phenotype. The Rank 4 FAS facial phenotype determined with the 4-Digit Diagnostic Code requires the presence of all three of the following anomalies: (i) palpebral fissure length 2 or more SDs below the norm; (ii) smooth philtrum (Rank 4 or 5 on the Lip-Philtrum Guide), an (iii) thin upper lip (Rank 4 or 5 on the Lip-Philtrum Guide). Examples of the Rank 4 FAS facial phenotype for Caucasian, Native American, African American, and Asian American children are shown. © Susan Astley. FASD, fetal alcohol spectrum disorder; FAS, fetal alcohol syndrome; CNS, central nervous system.

by a wide variety of diagnostic teams in United States and other countries. The control population for this study was selected primarily from a large cohort of children enrolled at birth in a University of Washington study of typical development conducted through the Department of Speech and Hearing Sciences. With the enrollment of each child in the FAS/partial FAS (PFAS) group, a child matched on age (within 6 months), gender, and race was randomly identified and invited to enroll from the eligible SE/AE, ND/AE, and Control populations. The enrollment goal was 80 subjects (20 per group).

The study enrollment procedure produced a sample of 81 children of diverse ethnicity. The age range (8 to 15.9 years) included the broadest age range of children that could be administered a comparable psychometric assessment battery and be reasonably capable of participating in the MR scanning. Each of the 4 study groups had 16 to 24 subjects successfully balanced on age, gender, and race. The 61 children with FASD were highly representative of the entire clinic sample of 1,200 from which they were drawn. The clinic population of 1,200 was 43% female, 51% Caucasian, with 40% between 8 and 15.9 years of age. The 4-Digit Codes of all 81 children were presented in the neuropsychological/behavioral report for this study (Astley et al., 2009b). The diagnostic features specific to each group are as follows:

1. Children in Group 1 had a 4-Digit diagnosis of FAS/PFAS (e.g., 4-Digit Diagnostic Categories A, B, C: with Growth Ranks 1–4, Face Ranks 3–4, CNS Ranks 3 and/or 4, and Alcohol Ranks 2–4) (Fig. 1). Alcohol Rank 2 (unknown exposure) could only be present if the child had a diagnosis of full FAS because the Rank 4 FAS facial features are so specific to prenatal alcohol exposure (Astley and Clarren, 1996; Astley et al., 2002). As the only clinical difference between FAS and PFAS in this study was the presence of growth deficiency in the former, FAS and PFAS were combined. In summary, children in Group 1 had severe cognitive/behavioral dysfunction and the FAS facial phenotype.
2. Children in Group 2 had a 4-Digit diagnosis of SE/AE (e.g., 4-Digit Diagnostic Categories E and F: with Growth Ranks 1–4, Face Ranks 1–2, CNS Ranks 3 and/or 4, and Alcohol Ranks 3–4). In summary, children in Group 2 had severe cognitive/behavioral dysfunction, comparable with Group 1, but did not have the FAS facial phenotype.
3. Children in Group 3 had a 4-Digit diagnosis of ND/AE (e.g., 4-Digit Diagnostic Categories G and H: with Growth Ranks 1–4, Face Ranks 1–2, CNS Rank 2, and Alcohol Ranks 3–4). In summary, children in Group 3 had prenatal alcohol exposure like Groups 1 and 2, but had only mild to moderate cognitive/behavioral dysfunction, and did not have the FAS facial phenotype.
4. Children in Group 4 (Healthy Controls/No Alcohol Exposure) were selected based on parental report that the child was healthy, had no academic concerns, and no prenatal alcohol exposure (e.g., 4-Digit Diagnostic Category V: with Growth Ranks 1–2, FAS Face Ranks [no restrictions], CNS Rank 1, Alcohol Rank 1). In summary, these were nonexposed, healthy, average to high-functioning controls.

Using the FASD terminology introduced by Stratton and colleagues (1996), the SE/AE and ND/AE groups most closely reflected the severe and mild expressions of ARND, respectively. A comprehensive analysis of the between-group differences of these diagnostic features is presented in the neuropsychological/psychiatric report for this study (Astley et al., 2009b).

Within our FASD participants, 1 subject with PFAS had agenesis of the corpus callosum (ACC) and 1 subject with FAS had hypogenesis of the corpus callosum (HCC). That these subjects had callosal abnormalities was known prior to study enrollment. Indeed these 2 subjects with ACC/HCC were the only documented cases of ACC/HCC in the 2,040 patients with prenatal alcohol exposure diagnosed to date at the WA State FAS DPN clinics. MRIs were typically only available when clinically indicated (e.g., evidence of neurological abnormalities). As such, only 204 (10%) of the 2,040 patients evaluated at the FAS DPN had a previous MRI evaluation summarized in their medical record and 76% of the 204 MRI evaluations were interpreted as normal by the patient's neuroradiologist. Although ACC/HCC has been observed in individuals with FASD (Riley et al., 1995), ACC/HCC is not specific to prenatal alcohol exposure. The prevalence of ACC among developmentally disabled populations is estimated to be 2 to 3 per 100 (Jeret et al., 1986). Thus, a causal link between ACC/HCC and prenatal alcohol exposure in these 2 individuals should not be assumed nor can it be ruled out. As all current FASD diagnostic guidelines (Astley, 2004; Bertrand et al., 2004; Chudley et al., 2005; Hoyme et al., 2005) list ACC/HCC as one of the many types of structural abnormalities that meet the CNS criteria for a FAS/PFAS diagnosis, it would be clinically invalid to exclude ACC/HCC from the FAS/PFAS study group. While they might represent a very small fraction of all alcohol-exposed patients evaluated in the FAS DPN clinic, they represent 2 of all 41 patients with FAS/PFAS from the FAS DPN clinic who met the 8- to 15-year-old eligibility criteria for enrollment into this study.

Study Participation

Participation in the study involved 5 visits over a 4- to 6-week study period. The psychological and sociodemographic data were collected during visits 1 and 2. The MR data were collected during visits 3 and 4. Outcomes of the psychological assessments were shared with the caregivers on visit 5, and submitted to the child's medical record with caregiver consent.

Sociodemographic and Clinical Assessments

A comprehensive sociodemographic and health/medication history of each child was obtained by parent interview and record review. Information included birth data, growth, and all prenatal and lifetime exposures and adverse events. For subjects with FASD, most information was obtained at the time of their FASD diagnostic evaluation. All controls had a reported absence of prenatal alcohol exposure. All children had a standardized digital facial photograph taken at the time of enrollment. The facial photographs were analyzed using the FAS Facial Analysis Software (Astley, 2003) to document the magnitude of expression of the FAS facial phenotype (Astley and Clarren, 1996). A more detailed methodology and analysis of the sociodemographic and FASD diagnostic outcomes, including prenatal alcohol exposure histories, were presented in the neuropsychological/behavioral report from this study (Astley et al., 2009b).

Neuropsychological and Psychiatric Assessments

A detailed description of the assessment battery and a comprehensive analysis of the between-group differences in neuropsychological outcome were presented in the neuropsychological/behavioral report for this study (Astley et al., 2009b). Briefly, a comprehensive, standardized assessment battery was administered to each child and their primary caregiver by a psychologist masked to group assignment. The assessment battery was designed to capture the domains of potential neuropsychological impairment seen as the result of the typically diffuse brain damage arising from alcohol teratogenesis (Bertrand et al., 2004; Chudley et al., 2005; Kodituwakku, 2007; Mattson and Riley, 1998; Olson et al., 1998; Roebuck et al., 1999). The neuropsychological/behavioral outcomes served to profile the study groups and confirm the groups were clinically and statistically distinct from one another; fundamental to the interpretation of the MR outcomes. The neuropsychological data will also be used to

assess correlations between brain structure and function. These correlations will be reported separately.

It is important to note that the mean full scale IQ of the healthy Control group (123 ± 7 SD) was higher than the population-based mean of 100 ± 15 SD. This was anticipated as children with potential threats to brain development were screened out and recruitment was through a University community. Other population-based MRI and FASD-MRI studies enrolling healthy controls have reported mean FSIQs ranging from 110 to 127 (Bookstein et al., 2002b; Haier et al., 2004; Sowell et al., 2008; Waber et al., 2007). Most FASD-MRI studies do not report the IQ or neuropsychological profile of their healthy control population. In spite of the Control group's relatively high IQ, however, many of the memory, executive function, language, and adaptive behavior scores assessed for this Control group were, on average, solidly within normal limits compared with age peers (Table 1) (Astley et al., 2009b). The ND/AE group had a mean FSIQ (99.2 ± 11.3 SD) equivalent to the population-based mean, despite their multiple prenatal/postnatal risk factors and significant adaptive/behavioral deficits.

MR Scanner

All scans (MRI, MRS, and fMRI) were acquired using a General Electric 1.5 Tesla scanner in the Diagnostic Imaging Sciences Center at the University of Washington.

MRS and fMRI

The MRS (Astley et al., 2009c) and fMRI (Astley et al., 2009a) components of this study were reported separately. Briefly, MRS was used to measure the concentrations of neurometabolites, including: (i) choline, a marker of cell membrane stability and myelination, (ii) *N*-acetyl aspartate, a neuronal or axonal marker, and (iii) creatine, a marker of metabolic activity, in selected brain regions. fMRI was used to assess neuroactivation in selected brain regions during performance of N-back working memory tasks.

Structural MRI Acquisition

An initial sagittal series was obtained first for orientation of subsequent series (Echo Time (TE) = 8, Time to Repetition (TR) = 400, flip angle = 25°, Field of View (FOV) = 24 × 24, matrix = 256 × 160, thickness = 4.0 mm, gap = 1.0 mm]. A high resolution 3-D T1-weighted fast gradient echo image of the whole brain was then performed in the axial plane [TE = 3, TR = 18, FOV = 24 × 18, matrix = 256 × 256, number of excitations (NEX) = 2, thickness = 1.5 mm, no gap]. This acquisition allowed images to be reformatted into any plane, which, in turn, allowed measurement of each structure in the plane that was optimal for its visualization. This also allowed brain scans to be realigned to ensure that all scans were measured in a standardized format. An exact midsagittal slice was reconstructed, allowing for area measures of corpus callosum and cerebellar vermis. Total scanning time for the structural series was approximately 15 minutes. Each scan was clinically reviewed by the neuroradiologist (masked to group assignment) to determine if there were any gross structural abnormalities.

Structural MRI Image Processing

Magnetic resonance imaging measures were performed on a PC workstation using the MEASURE program (The Johns Hopkins University, Baltimore, MD) (Barta et al., 1997). Each scan was rotated in 3-D space so that the axial images were parallel to the line connecting the anterior and posterior commissures and perpendicular to the interhemispheric fissure (ac–pc plane). Coronal slices were reconstructed with a thickness of 0.9375 mm and positioned perpendicular to the ac–pc plane. Based on prior FASD MRI literature (Archibald et al., 2001; Mattson et al., 2001; Miller et al., 1999; Sowell et al., 2001b), volume measurements focused on the hippocampus, caudate, putamen, frontal lobe, gray matter and white matter of the frontal lobe, and total brain volume from the 1.5 mm spoiled gradient recalled echo in steady state (SPGR). Area measures included cerebellar vermis and its subregions, corpus callosum and its subregions, and total brain area in the midsagittal slice. For the hippocampus, caudate, putamen, and frontal lobe volume measures, area of each structure was outlined manually, using a mouse-controlled cursor, in each slice. Areas within each slice were calculated, summed across slices, and multiplied by slice thickness, resulting in approximate structure volumes. Semi-automated methods were used to measure total brain volume and a stereology point-counting method was used to measure gray and white matter within the frontal lobe. Specific methods of measurement for each structure are mentioned below.

Hippocampus. The rules for defining boundaries of the hippocampus were developed by Aylward and colleagues (1999). Briefly, measurement was made on the reconstructed coronal slices, began in the most posterior coronal slice in which the hippocampus was viewed. Boundaries of the hippocampus were traced manually, with the choroid fissure as the superior boundary, the inferior temporal horn of the lateral ventricle as the lateral boundary, and the white matter of the parahippocampal gyrus as the inferior boundary. The hippocampus formed a natural boundary around the edge of the medial temporal lobe. Both the alveus and the subiculum were included in hippocampal measurements. Anteriorly, when a clear demarcation between the hippocampus and amygdala was not seen coronally, the sagittal view was consulted to determine the border between the hippocampus and amygdala. Interrater reliability for the hippocampus yielded an intraclass correlation of 0.92.

Basal Ganglia. Volumes of putamen and caudate were obtained on the axial images using rules previously described (Aylward et al., 1997a). Briefly, measurement of putamen and caudate began in the most inferior slice in which these structures were clearly separated by the internal capsule. Measurement continued in a superior direction until the body of the caudate was no longer observed. The borders of the caudate were defined laterally by the anterior limb of the internal capsule and medially by the frontal horn or body of the lateral ventricle. The borders of the putamen were defined laterally by the external capsule. At more inferior levels, the medial borders of the putamen were defined by the globus pallidus; at more superior levels, the medial borders were defined by the internal capsule. Intrarater reliability yielded intraclass correlations of 0.99 for both caudate and putamen. Interrater reliability yielded intraclass correlations of 0.97 for caudate and 0.94 for putamen.

Frontal Lobe Volume. The procedure used to measure the volume of the frontal lobes (Aylward et al., 1997b) and of the gray and white matter within the frontal lobes was based on the identification of sulcal-gyral landmarks on the surface of a 3-D reconstruction of the 1.5 mm coronal slices. For frontal lobe measures, this 3-D reconstruction which could be viewed in any orientation, was used to identify the precentral gyrus and sylvian fissure. Using the MEASURE software, the surfaces of these regions were "painted" on the 3-D reconstruction. The brain imaging data were then resliced in the axial plane, starting at the most superior level, and the paint (which remains on the surface of the recreated slices) was used to guide as the rater cut away portions of the brain posterior to the paint. Interrater reliability yielded an intraclass correlation of 0.99 for frontal lobe volume. After the frontal lobe was thus identified, a stereological point-counting method was used to measure gray and white volumes within the frontal lobe, as described by Aylward and colleagues (1995). Interrater reliability yielded an intraclass correlation of 0.92 for the frontal cortex.

Table 1. Sociodemographic and FASD 4-Digit Diagnostic Code Profiles of the 4 Study Groups

	Groups								Statistics			
									ANOVA			
	1. FAS/PFAS[a]		2. SE/AE		3. ND/AE		4. Control		Overall	Post hoc	A priori LT	Chi-squared test
Characteristic	*n* = 20		*n* = 24		*n* = 21		*n* = 16		*F* (*p*)[b]	Duncan	*F* (*p*)[c]	Chi (*p*)
Gender: *n* (%)												
Female	10	50.0	8	33.3	10	47.6	8	50.0				1.7 (0.63)
Age at enrollment in years: mean (SD)	12.7	2.4	12.2	2.0	12.4	2.3	12.4	2.7	0.1 (0.96)		0.1 (0.79)	
Race: *n* (%)												
Caucasian	12	60.0	11	45.8	12	57.1	13	81.3				[d]5.0 (0.17)
African American	6	30.0	4	16.7	6	28.6	2	12.6				
Native American	2	10.0	7	29.2	2	9.5	0	0.0				
Other	0	0.0	2	8.3	1	4.8	1	6.3				
Growth rank from 4-Digit Code: *n* (%)												
1. None	10	50.0	15	62.5	13	61.8	15	93.7				[e]10.3 (0.02)
2. Mild	2	10.0	2	8.3	6	28.6	1	6.3				
3. Moderate	5	5.0	3	12.5	1	4.8	0	0.0				
4. Severe	3	15.0	4	16.7	1	4.8	0	0.0				
Current height percentile: mean (SD)	33.5	31.6	40.7	30.4	34.7	30.9	60.6	34.2	2.7 (0.05)	132,24	5.2 (0.03)	
Current weight percentile: mean (SD)	51.7	33.4	50.4	34.2	46.6	31.2	67.6	24.5	1.5 (0.22)		1.7 (0.19)	
Face Rank from 4-Digit Code: *n* (%) [c]												
1. None	0	0.0	4	16.7	7	33.3	10	62.5				
2. Mild	0	0.0	20	83.3	14	66.7	6	37.5				
3. Moderate	4	20.0	0	0.0	0	0.0	0	0.0				
4. Severe	16	80.0	0	0.0	0	0.0	0	0.0				
Facial *D*-Score	1.2	0.9	−0.4	0.9	−0.8	0.7	−1.5	0.9	31.6 (0.000)	1,23,4	84.4 (0.000)	
CNS Ranks 1–3 from 4-Digit Code												
Level of functional impairment: *n* (%)												
1. None	0	0.0	0	0.0	0	0.0	16	100				
2. Moderate	0	0.0	[f]3	12.5	21	100	0	0.0				
3. Severe	20	100	21	87.5	0	0.0	0	0.0				
CNS Rank 4 from 4-Digit Code												
Structural/Neurologic abnormality: *n* (%)												
Present	13	65.0	6	25.0	0	0.0	0	0.0				[g]31 (0.000)
Microcephaly (OFC ≤ −2 SD): *n*, %	10	50.0	2	8.3	0	0.0	0	0.0				[H]26(0.000)
Alcohol Rank from 4-Digit Code: *n* (%)												
1. No exposure	0	0.0	0	0.0	0	0.0	16	100				
2. Unknown exposure	1	5.0	0	0.0	0	0.0	0	0.0				
3. Confirmed exposure, level: moderate or Unk	7	35.0	12	50.0	11	52.4	0	0.0				
4. Confirmed exposure, level: high	12	60.0	12	50.0	10	47.6	0	0.0				
Alcohol use prior to pregnancy												
Days per week: mean (SD), range	5.4 (1.7)	2–7	4.0 (2.2)	1–7	5.3 (2.1)	1–7	0.9 (1.0)	0–3	19.8 (0.000)	123,4	31.0 (0.000)	
Most drinks/occasion: mean (SD), range	23.1 (24.8)	8–78	19.8 (26.3)	2–96	12.7 (7.7)	4–24	1.7 (1.5)	0–5	3.8 (0.018)	123,4	8.7 (0.005)	

Table 1. (Continued)

	Groups								Statistics			
									ANOVA			
	1. FAS/PFAS[a]		2. SE/AE		3. ND/AE		4. Control		Overall	Post hoc	A priori LT	Chi-squared test
Characteristic	*n* = 20		*n* = 24		*n* = 21		*n* = 16		*F* (*p*)[b]	Duncan	*F* (*p*)[c]	Chi (*p*)
Alcohol use during pregnancy												
Days per week: mean (SD), range	5.5 (1.7)	3–7	3.9 (2.1)	1–7	5.3 (2.1)	1–7	0 (0)	0–0	35.9 (0.000)	123,4	35.8 (0.000)	
Most drinks/occasion: mean (SD), range	11.6 (7.1)	5–24	14.1 (8.9)	3–26	11.7 (7.3)	4–24	0 (0)	0–0	14.2 (0.000)	123,4	17.8 (0.000)	
Drank all 3 trimesters: *n* (valid %)	13	77	13	59	7	50.0	0	0.0				21 (0.000)
Neuropsychological selected tests	Mean	SD	Mean	SD	Mean	SD	Mean	SD				
WISC-III: FSIQ (ss)	77.5	14.4	79.3	10.5	99.2	11.3	123.9	6.5	67.6 (0.000)	12,3,4	183.4 (0.000)	
VABS: adaptive behavior composite (ss)	59	17.5	55	14.2	65.4	21.1	95.3	12.3	21.1 (0.000)	123,4	46.3 (0.000)	
D-KEFS: Tower, Total Achievement (ss)	7.6	2.3	8.3	2.5	9.6	2.1	10.8	2.1	7.0 (0.000)	12,23,34	20.5 (0.000)	
VMI: Total (ss)	76.2	12.7	81.4	9.2	90.9	11.8	102.7	12.9	17.8 (0.000)	12,3,4	51.6 (0.000)	

Chi2: chi-square test across four study groups, unless otherwise specified. D-KEFS: Delis-Kaplan Executive Function System, Tower, Total Achievement (Delis et al., 2000). Duncan: Multiple comparison range test. Reported if the overall ANOVA is statistically significant. Commas separate groups with homogeneous means at $p < 0.05$. F: *F* statistic. LT: ANOVA unweighted linear trend. OFC: occipital frontal circumference. Overall: Overall assessment of between-group means using ANOVA. *p*: *p* value. SD: standard deviation. Unk: unknown. VABS: Vineland Adaptive Behavior Scales, Adaptive Behavior Composite (Sparrow et al., 1984). VMI: Beery Buktenica Developmental Test of Visual-Motor Integration (Beery, 1997). WISC-III Full Scale IQ (Wechsler, 1996).

[a]Six of the 20 subjects in Group 1 had full FAS using the 4-Digit Code. Ten of the 14 PFAS had Rank 4 Faces but received a diagnosis of PFAS because they had no growth deficiency (Growth Rank 1).

[b]Between-groups, df = 3; within-groups, df = total sample size − 4.

[c]Between-groups linear term df = 1; within-groups df = total sample size − 4.

[d]Caucasian versus not Caucasian.

[e]No growth deficiency versus mild to severe growth deficiency.

[F]All 3 children with moderate functional impairment had structural evidence of brain abnormality (microcephaly).

[G]FAS/PFAS versus SE/AE ($\chi^2 = 7.1$, $p = 0.008$).

[H]FAS/PFAS versus SE/AE ($\chi^2 = 9.6$, $p = 0.002$).

Total Brain Volumes. Regional volumes were divided by total brain volume to allow correction for overall brain size. Total brain volume was measured using semi-automated thresholding procedures for segmenting brain tissue from cerebral spinal fluid (CSF) on the 1.5 mm axial images. Briefly, this procedure allowed the user to set the contrast such that all pixels above a certain value were highlighted, thus eliminating CSF (which in these images was black). A mask of this region was saved, and a command of "erode" was executed that "shrunk" the highlighted areas by a specified number of pixels. This performed automatic cutting of "bridges" between highlighted brain and nonbrain (e.g., dura and muscle) tissue regions. The cursor was then placed inside the brain region, and an "isolate blob" command then identified only those pixels that were connected (in any plane) with the pixel at the cursor location. This allowed the brain to be isolated from nonbrain tissue. Finally, a "dilate" command was executed, which restored pixels that were eroded previously, but no further than the original mask. Raters modified the procedure to ensure that only nonbrain tissue was removed. Intrarater reliability for obtaining brain volumes with this procedure yielded an intraclass correlation of 0.99. At each step, modifications were made manually to ensure inclusion of all brain tissue and exclusion of nonbrain regions.

Midsagittal Area Measures. The 3-D brain was rotated so that the interhemispheric fissure was perfectly positioned in the vertical plane. As described above, the slices were reformatted from the 1.5 mm axial series, yielding sagittal slices that were 0.9375 mm thick. The sagittal slice yielding the clearest visualization of the cerebral aqueduct was selected for the midsagittal measures. Midsagittal area measures were performed for cerebellar vermis and its 3 subsections (Lobules I–V, Lobules VI–VII, and Lobules VIII–X), corpus callosum and 5 subregions, and total brain (Aylward and Reiss, 1991; Aylward et al., 1994; Reiss et al., 1991). Interrater reliability for obtaining midsagittal areas yielded intraclass correlations ranging from 0.87 to 0.94. Midsagittal area of the total brain was also measured to allow correction of the corpus callosum and cerebellar vermis measures for overall brain size. The corpus callosum (CC) length (cm) was the distance from the most anterior and posterior borders of the CC that intersected with a line perpendicular to the ac–pc plane. The CC was transected into 5 equiangular regions: (i) genu, (ii) anterior body, (iii) posterior body, (iv) isthmus, and (v) splenium, using the mammillary body as a reference point (Riley et al., 1995).

MRI Hypotheses

In this report the analyses focus on the MRI comparisons between the 4 study groups. The following primary hypotheses were derived from the current MRI FASD literature (Archibald et al., 2001; Astley and Clarren, 2001; Bookstein et al., 2002b; Mattson et al., 2001; Miller et al., 1999; Sowell et al., 2001b). Note again that the neuropsychological/psychiatric report for this study (Astley et al., 2009b) confirmed that the 4 study groups were clinically distinct and increasingly more affected progressing across the 4 groups from the Controls to the FAS/PFAS.

1. The mean absolute and/or relative size of the brain as a whole and its regions would become increasingly smaller progressing across the 4 study groups from Controls to ND/AE to SE/AE to FAS/PFAS.
2. The mean absolute and/or relative size of the brain as a whole and its regions would be significantly smaller in the FAS/PFAS group (with the FAS facial phenotype) compared with the SE/AE group (without the FAS facial phenotype). This hypothesis specifically addressed a common clinical question: did individuals with FASD and the FAS facial phenotype have more severe brain abnormality than individuals with FASD and no FAS facial phenotype?
3. The prevalence of subjects with 1 or more brain regions 2 or more SDs below the mean size of the Control group would increase significantly progressing from the ND/AE group to the SE/AE group and to the FAS/PFAS group.

Statistical Analysis

The statistical analyses used to confirm the 4 study groups, effectively balanced on age, gender, and race, were described and presented in the neuropsychological/psychiatric report (Astley et al., 2009b).

Primary Analyses. ANOVA was used to determine if differences in mean size of brain regions existed among the 4 study groups. If significant differences existed, the Duncan post hoc range test was used to identify which group mean differed. The Duncan test makes pairwise comparisons using a stepwise procedure. Mean was ordered from highest to lowest, and extreme differences were tested first. The Duncan test sets a protection level for the error rate for the collection of tests and identifies homogeneous subsets of mean that are not different from one another at the $p = 0.05$ level. To specifically test primary hypothesis 1, an a priori test for linear trend was included in the ANOVA to determine if the mean size of selected brain regions became increasingly smaller progressing across the 4 study groups from Control to ND/AE to SE/AE to FAS/PFAS. To test primary hypothesis 2, an a priori contrast (*t*-test) between the FAS/PFAS and SE/AE groups was specified in the ANOVA. To test primary hypothesis 3, a chi-squared test for trend was used to compare the prevalence of structural anomalies across the 3 FASD groups relative to the Control group. Two-tailed *p* values of 0.05 were used throughout the analyses.

Secondary Analyses. Secondary analyses using Pearson Correlations coefficients and ANOVA tests for linear trends were conducted to determine if the size of brain regions decreased with increasing quantity, frequency, and/or duration of reported prenatal alcohol exposure between the 3 FASD groups. Two adjustments were used throughout the analysis of the MRI data: (1) adjustment for total brain volume (or midsagittal area) and (2) inclusion or exclusion of the 2 subjects in the FAS/PFAS group with ACC/HCC (Fig. 2*A* and 2*B*). Adjustment 1: to determine if some brain regions were disproportionately reduced in size. Given that overall brain size was often reduced among individuals with prenatal alcohol exposure, relative measures of brain regions were computed by dividing the volume of the region by total brain volume, or the midsagittal area of the brain region by the midsagittal area of the total brain. The terms "relative" and "absolute" were used to distinguish the 2 types of measures. Adjustment 2: the 2 subjects with ACC/HCC in FAS/PFAS group had CCs that were substantially smaller than the CCs of the other members of that group. The midsagittal area of the CC was 0.3 cm^2 in the subject with agenesis and 1.95 cm^2 in the subject with hypogenesis (Figs. 2*A* and 2*B*). These are 6 and 42%, respectively, of the mean midsagittal area of the CC (4.64 cm^2) for the remaining 18 members of the FAS/PFAS group. Inclusion of these 2 subjects in the FAS/PFAS group could influence some between-group differences (particularly differences in the mean midsagittal area of the CC). As such, it was important to confirm statistically significant group differences were not driven primarily by these 2 lowest measures (which represent outliers in the FASD sample). Although the size of the CC for the subject with ACC was a statistical outlier (more than 2 SDs below the mean of the FAS/PFAS group), it would not be clinically valid to exclude this case from the study. All current published FASD diagnostic guidelines (Astley, 2004; Bertrand et al., 2004; Chudley et al., 2005; Hoyme et al., 2005) list ACC as an example of a CNS structural abnormality that meets the CNS diagnostic criteria for FASD. Thus, all analyses were conducted

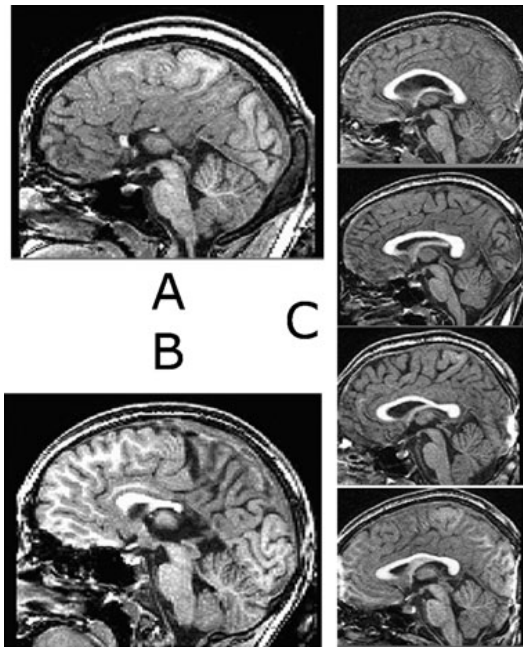

Fig. 2. Two subjects with (**A**) agenesis and (**B**) hypogenesis of the corpus callosum in the fetal alcohol syndrome (FAS)/partial FAS group. (**C**) Variability in corpus callosum shape among Controls with no prenatal alcohol exposure.

with inclusion of these 2 subjects. If their exclusion resulted in a statistical outcome that was discordant with the statistical outcome when the 2 subjects were included, both analyses are presented.

Power/Sample Size. This study had 80% power or greater to detect the following effect sizes at a two-tailed alpha level of 0.05: (i) a difference in 2 means equal to or greater than the SD of the mean difference; (ii) a correlation coefficient of 0.30 or greater; and (iii) a 35-point or greater difference in proportions between 2 groups.

RESULTS

Size of Brain Regions Across the 4 Groups (Primary Hypotheses 1–2)

Total Brain. The mean total brain volume decreased significantly progressing across the 4 study groups from Control to ND/AE to SE/AE to FAS/PFAS (Table 2). The linear trend remained significant with exclusion of the Control group, confirming that total brain size decreased incrementally across the 3 FASD groups. Indeed, all significant linear trends by brain region, reported in Table 2, remained significant with exclusion of the Control group. The mean total brain volume of the FAS/PFAS group was significantly smaller (11% smaller) than the mean of the Control group. The prevalence of microcephaly (occipital frontal circumference ≤−2 SD) was significantly higher in the FAS/PFAS group with the FAS facial phenotype than in the SE/AE group without the FAS facial phenotype (83.1% vs. 16.7%; $\chi^2 = 7.6$, two-tailed $p = 0.006$) (Astley et al., 2009b). This group difference was not influenced by the 4-Digit Code diagnostic criteria for CNS abnormality. The CNS criteria for FAS, PFAS, and SE/AE were identical (e.g., presence of structural and/or significant functional abnormality). Was brain size reduced simply because individuals with FASD were typically growth deficient? Although FAS is the only FASD subclassification in the 4-Digit Code that requires the presence of some level of growth deficiency (height and/or weight below the 10th percentile), all 3 FASD groups were significantly shorter in stature (but not lower in weight) than the Controls (Table 1). Despite the growth deficiency among the FASD, there was no significant correlation between height or weight percentile and total brain size across the 81 subjects.

Frontal Lobe. Absolute Volume: The mean absolute volume of the frontal lobe decreased incrementally and significantly, progressing across the 4 study groups from Controls to FAS/PFAS (Table 2). The mean absolute volume of the frontal lobe for the FAS/PFAS group was significantly smaller (11–18% smaller) than each of the other groups.

Relative Volume: The mean relative volume of the frontal lobe decreased significantly progressing across the 4 study groups from Control to FAS/PFAS (with and without inclusion of the 2 subjects with ACC/HCC). The mean volume of the frontal lobe for the FAS/PFAS group with the 2 subjects with ACC/HCC removed was 352.3 (62.1 SD). When the subjects with ACC/HCC were included in the FAS/PFAS group, no significant pair-wise group differences were observed. When the 2 subjects with ACC/HCC were excluded from the FAS/PFAS group, the mean relative volume of the frontal lobe for the FAS/PFAS group was significantly smaller (6–9% smaller) than each of the 3 other groups.

Gray/White Matter: The mean absolute volume of white and gray matter in the frontal lobe decreased significantly progressing across the 4 study groups from Control to ND/AE to SE/AE to FAS/PFAS. The mean absolute volume of the frontal gray matter for the FAS/PFAS group was also significantly smaller (19% smaller) than the mean of the SE/AE group. The mean percent white matter and percent gray matter in the frontal lobes were comparable across the 4 study groups.

Caudate. Absolute Volume: The mean absolute volume of the caudate decreased significantly progressing across the 4 study groups from Control to FAS/PFAS. The mean absolute volume of the caudate in both the FAS/PFAS and SE/AE groups were comparable with one another but significantly smaller (on average 23 and 19% smaller, respectively) than the mean of the Control group (Table 2).

Relative Volume: The mean relative volume of the caudate in both the FAS/PFAS and SE/AE groups were comparable with one another and significantly smaller (12 and 14%, respectively) than the mean of the Control group. No differences in absolute or relative size were observed between the right and left caudate.

Table 2. Mean Size of Brain Regions Across the 4 Study Groups

	Group												ANOVA			
	1. FAS/PFAS			2. SE/AE			3. ND/AE			4. Control			Overall	Post Hoc	A Priori Contrasts LT	Groups 1vs2[a]
Brain Region	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*F* (*p*)[b]	Duncan[a]	*F* (*p*)[c]	*T* (*p*)[c]
Total brain volume (cm^3)	20	1217.8	183.4	24	1284.7	180.0	21	1305.0	95.1	16	1370.5	99.3	3.2 (0.03)	123,234	9.3 (0.003)	1.5 (0.14)
Total brain midsaggital area (cm^2)	20	6.7	0.8	24	7.1	0.8	21	7.2	0.4	14	7.6	0.7	5.0 (0.003)	12,234	14.1 (0.000)	2.1 (0.04)
Frontal lobe volume (cm^3)	19	346.1	61.7	23	385.7	59.7	20	391.3	41.1	16	419.8	45.6	5.7 (0.001)	1,234	16.0 (0.000)	2.4 (0.02)
Frontal lobe/total brain[d]	17	0.283	0.03	23	0.301	0.03	20	0.300	0.02	16	0.306	0.02	3.0 (0.03)	1,234	5.4 (0.02)	2.0 (0.05)
Frontal lobe/total brain	19	0.286	0.03	23	0.301	0.03	20	0.300	0.02	16	0.306	0.02	1.9 (0.14)		4.5 (0.04)	
Frontal lobe gray matter volume (cm^3)	19	190.6	38.1	22	216.2	33.7	20	220.8	28.6	15	235.4	28.3	5.7 (0.001)	1,234	15.5 (0.000)	2.5 (0.01)
Frontal lobe % gray matter	19	0.550	0.04	22	0.564	0.03	20	0.563	0.04	15	0.559	0.03	0.7 (0.53)		0.5 (0.50)	
Frontal lobe white matter volume (cm^3)	19	155.4	28.6	22	167.5	31.8	20	171.0	22.9	15	186.0	24.7	3.5 (0.002)	123,234	10.3 (0.002)	1.4 (0.17)
Frontal lobe % white matter	19	0.450	0.04	22	0.436	0.03	20	0.437	0.04	1	0.441	0.03	0.7 (0.53)		0.5 (0.50)	
R. Caudate volume (cm^3)	19	3.8	0.5	24	3.9	0.9	21	4.5	0.4	16	4.8	0.5	12.2 (0.000)	12,34	33.7 (0.000)	0.7 (0.46)
L. Caudate volume (cm3)	19	3.7	0.5	24	3.9	0.9	21	4.4	0.6	16	4.8	0.6	10.2 (0.000)	12,3,4	29.4 (0.000)	0.9 (0.36)
Total caudate volume (cm^3)	19	7.4	1.0	24	7.8	1.7	21	8.8	0.9	16	9.6	1.1	11.6 (0.000)	12,34	32.8 (0.000)	0.9 (0.39)
Total caudate/total brain (10^{-2})	19	0.618	0.09	24	0.608	0.12	21	0.679	0.78	16	0.705	0.86	4.6 (0.005)	12,23,34	10.5 (0.002)	0.4 (0.73)
Caudate + putamen volume (cm^3)	19	14.0	2.3	24	15.2	2.6	21	16.4	1.8	16	17.2	2.0	7.2 (0.000)	12,23,34	8.8 (0.04)	1.8 (0.08)
R. Putamen volume (cm^3)	19	3.3	0.8	24	3.7	0.9	21	3.8	0.6	16	3.8	0.7	2.3 (0.08)		5.2 (0.03)	
L. Putamen volume (cm^3)	19	3.3	0.8	24	3.8	0.7	21	3.8	0.7	16	3.7	0.7	1.8 (0.15)		2.7 (0.11)	
Total putamen volume (cm^3)	19	6.6	1.5	24	7.4	1.6	21	7.6	1.2	16	7.6	1.3	2.9 (0.04)	12,234	4.4 (0.04)	2.0 (0.04)
Total putamen volume (cm^3)[d]	17	6.7	1.5	24	7.4	1.6	21	7.6	1.2	16	7.6	1.3	1.7 (0.18)		3.4 (0.07)	
Total putamen/total brain (10^{-2})	19	0.546	0.12	24	0.582	0.12	21	0.584	0.09	16	0.550	0.08	0.8 (0.53)		0.1 (0.91)	
R. Hippocampus volume (cm^3)	20	2.9	0.5	24	3.0	0.4	21	3.1	0.5	16	3.4	0.5	5.1 (0.003)	123,4	14.7 (0.000)	1.0 (0.29)
L. Hippocampus volume (cm^3)	20	2.9	0.5	24	2.9	0.4	21	3.1	0.4	16	3.4	0.6	4.5 (0.006)	123,4	12.6 (0.001)	0.5 (0.63)
Total hippocampus volume (cm^3)	20	5.7	1.0	24	5.9	0.8	21	6.2	0.8	16	6.8	1.0	5.1 (0.003)	123,4	14.6 (0.000)	0.8 (0.43)
Total hippocampus/total brain (10^{-2})	20	0.473	0.07	24	0.470	0.09	21	0.478	0.08	16	0.501	0.07	0.6 (0.64)		1.3 (0.26)	
CC: midsagittal area (cm^2)	20	4.12	1.3	24	4.45	0.8	21	4.35	0.7	16	4.64	0.7	1.0 (0.38)		2.3 (0.13)	
CC: Region 1 (genu) (cm^2)	20	1.15	0.4	24	1.21	0.3	21	1.19	0.2	16	1.34	0.2	1.5 (0.22)	123,234	3.6 (0.06)	
CC: Region 2 (cm^2)	20	0.74	0.2	24	0.76	0.2	21	0.72	0.1	16	0.76	0.2	0.2 (0.90)		0.1 (0.92)	
CC: Region 3 (cm^2)	20	0.63	0.2	24	0.64	0.1	21	0.63	0.1	16	0.70	0.1	0.6 (0.58)		1.4 (0.25)	
CC: Region 4 (cm^2)	20	0.55	0.2	24	0.62	0.1	21	0.61	0.2	16	0.63	0.2	0.8 (0.48)		1.6 (0.21)	
CC: Region 5 (splenium) (cm^2)	20	1.04	0.4	24	1.21	0.3	21	1.18	0.3	16	1.22	0.2	1.5 (0.23)		2.4 (0.13)	
CC: Length (cm)[d]	18	6.75	0.7	24	6.75	0.8	21	6.99	0.4	16	7.41	0.5	3.9 (0.01)	123,4	9.9 (0.002)	0.1 (0.99)
CC: Length (cm)	20	6.26	1.8	24	6.75	0.8	21	6.99	0.4	16	7.41	0.5	3.9 (0.01)	123,234	11.5 (0.001)	1.6 (0.13)
CC/brain midsaggital area	20	0.614	0.18	24	0.631	0.12	21	0.602	0.09	14	0.611	0.10	0.3 (0.83)		0.1 (0.80)	
CC/brain midsaggital area, Region 1 genu	20	0.171	0.05	24	0.171	0.04	21	0.165	0.03	16	0.175	0.02	0.3 (0.85)		0.1 (0.84)	
CC/brain midsaggital area, Region 2[d]	18	0.117	0.02	24	0.108	0.04	21	0.100	0.02	16	0.099	0.02	1.5 (0.22)		5.4 (0.02)	
CC/brain midsaggital area, Region 2	20	0.111	0.04	24	0.108	0.04	21	0.100	0.02	16	0.099	0.02	0.7 (0.57)		2.0 (0.16)	
CC/brain midsaggital area, Region 3	20	0.092	0.03	24	0.092	0.02	21	0.088	0.02	16	0.091	0.02	0.2 (0.93)		0.1 (0.71)	
CC/brain midsaggital area, Region 4	20	0.082	0.03	24	0.089	0.02	21	0.085	0.02	16	0.084	0.02	0.4 (0.44)		0.0 (0.96)	
CC/brain midsaggital area, Region 5	20	0.154	0.06	24	0.172	0.04	21	0.163	0.03	14	0.161	0.04	0.8 (0.49)		0.1 (0.79)	
Total CV: midsagittal area (cm^2)	20	7.4	0.8	24	8.4	1.6	21	7.9	1.3	16	8.4	1.6	3.4 (0.02)	13,234	5.2 (0.03)	2.7 (0.009)
CV: lobules I–V midsagittal area (cm^2)	20	2.9	0.4	24	3.3	0.5	21	3.1	0.4	16	3.4	0.5	5.4 (0.002)	13,23,24	8.2 (0.005)	3.3 (0.002)
CV: lobules VI–VII midsagittal area (cm^2)	20	2.1	0.4	24	2.4	0.6	21	2.4	1.0	16	2.4	0.5	1.1 (0.35)		1.9 (0.18)	
CV: lobules VIII–X midsagittal area (cm^2)	20	2.5	0.3	24	2.7	0.7	21	2.4	0.3	16	2.7	0.4	2.5 (0.07)		1.6 (0.21)	
Total CV/Brain midsaggital area	20	1.1	0.2	24	1.2	0.2	21	1.1	0.2	14	1.1	0.1	0.9 (0.41)		0.1 (0.79)	

CC, corpus callosum; CV, cerebellar vermis; L, left; R, right; T: *t* statistic from ANOVA a priori contrast; FAS, fetal alcohol syndrome; PFAS, partial FAS; SE, static encephalopathy; AE, alcohol exposed; ND, neurobehavioral disorder.

Duncan: multiple comparison range test; commas separate groups with homogeneous means at $p < 0.05$. LT: ANOVA unweighted linear trend across the four study groups. All significant linear trends remain significant with exclusion of the Control group.

[a]Only reported when overall ANOVA is statistically significant.

[b]Numerator degrees of freedom = 3; denominator df = total sample size minus 4.

[c]Numerator degrees of freedom = 1; denominator df = total sample size minus 4.

[d]Two subjects with agenesis and hypogenesis of the corpus callosum removed from FAS/PFAS group.

Putamen. Absolute Volume: The mean absolute volume of the putamen decreased significantly progressing across the 4 study groups from Control to FAS/PFAS (Table 2). This trend was no longer statistically significant ($F = 3.4$; df: 3,74; $p = 0.07$) after removal of the 2 subjects with ACC and HCC. The mean volume of the putamen for the FAS/PFAS group was significantly smaller (13% smaller) than the mean of the Control group. When the 2 subjects with ACC/HCC were excluded from the FAS/PFAS group, the mean volume of the putamen was 12% smaller than the mean of the Control group. This difference was no longer statistically significant ($t = 1.8$, $p = 0.08$).

Relative Volume: The mean relative volume of the putamen was comparable across all 4 study groups. No differences in absolute or relative size were observed between the right and left putamen.

Hippocampus. Absolute Volume: The mean absolute volume of the hippocampus decreased significantly progressing across the 4 study groups from Control to FAS/PFAS (Table 2). The mean absolute volumes of the hippocampus for each of the 3 FASD groups were significantly smaller (9–16% smaller) than the mean of the Control group.

Relative Volume: The mean relative volume of the hippocampus was comparable across the 4 study groups. No differences in absolute or relative size were observed between the right and left hippocampus.

Corpus Callosum. Absolute Area: The midsagittal area of the CC and each of the 5 subregions were 6–15% smaller in size (although not significantly) in each of the FASD groups relative to the Control group (Table 2). Exclusion of the 2 subjects with ACC/HCC did not alter these outcomes. When the 3 alcohol-exposed groups were combined, the mean midsagittal area of the genu (region 1) was significantly smaller (9%) (mean: 1.22 cm^2, 0.2 SD) relative to the Control group (mean: 1.34 cm^2, 0.2 SD) ($t = 2.0$; $p = 0.03$). This difference remained significant with exclusion of the 2 subjects with ACC/HCC. The mean absolute length of the corpus callosum decreased significantly progressing across the 4 study groups from Control to FAS/PFAS (with and without the ACC/HCC). The mean length of the corpus callosum for the FAS/PFAS group was significantly shorter (16%) than the mean of the Control group. The mean length of the corpus callosum for the FAS/PFAS group remained significantly shorter (9%) than the mean of the Control group after removal of the 2 subjects with ACC/HCC. Visual inspection of the CCs revealed substantial variability in the shape of the CC, even within the Control group (Fig. 2*C*).

Relative Area: The mean relative midsaggital area of the CC and its 5 subregions (after adjustment for total brain midsaggital area) were comparable across all 4 groups. When the 2 subjects with ACC/HCC were removed from the FAS/PFAS group, a significant increase in the relative size of Region 2 was observed, progressing across the 4 study groups from the Control group to the FAS/PFAS group.

Cerebellar Vermis. Absolute Area: The mean absolute midsagittal areas of the cerebellar vermis (CV) and lobules I–V were significantly smaller in the FAS/PFAS group (12 and 15%, respectively) than the mean of each area in the Control group (Table 2). Removal of the 2 subjects with ACC/HCC had no impact on these outcomes.

Relative Area: The mean relative midsagittal area of the CV and its 3 regions were comparable across all 4 groups.

Radiologist Review of MRI. Visual inspection of the study MRIs by the neuroradiologist on the investigative team identified the following prevalence of structural abnormalities: Control ($n = 0$, 0.0%), ND/AE ($n = 0$, 0.0%), SE/AE ($n = 3$, 12.5%), FAS/PFAS ($n = 3$, 15.0%). Three subjects in the FAS/PFAS presented with the following anomalies: 1 ACC, 1 HCC, and 1 with a 13 mm lesion in the left cerebellar hemisphere and slight deformity of the fourth ventricle. Three subjects in the SE/AE group presented with Chiari 1 malformations. Only the ACC and HCC were known to be present prior to the subjects' enrollment in the study. The neuroradiologist was masked to the subject's FASD diagnosis and study group assignment.

Size of Brain Regions Between FASD Subjects With and Without the FAS Facial Phenotype (Primary Hypothesis 2)

The mean absolute size of the frontal lobe, putamen, hippocampus, and CV were significantly smaller in the FAS/PFAS group than the SE/AE group (Table 2). The children with FAS/PFAS also had disproportionately smaller frontal lobes than the children with SE/AE (Table 2, Fig. 3). It is important to note that the only diagnostic feature that distinguishes the FAS/PFAS group from the SE/AE group in this study is the presence of the FAS facial phenotype in the former. Both groups had comparably severe CNS dysfunction (Astley et al., 2009b). The FAS Facial *D*-Score is a continuous measure of the magnitude of expression of the FAS facial features: the higher the *D*-Score, the more severe the expression of the FAS facial features (Astley and Clarren, 2001). The size of the following brain regions decreased significantly (Pearson Correlation Coefficients with two-tailed p values < 0.05) as the FAS Facial *D*-Score increased: frontal lobe volume (absolute size: −0.261, relative size: −0.215); midsagittal area of cerebellar vermis (absolute size: −0.299); and caudate volume (absolute size: −0.362, relative size: −0.262).

Structural Abnormality Correlations With FASD Group and CNS Function (Primary Hypothesis 3)

The number of subjects in each FASD study group, with 1 or more brain regions that were 2 or more SDs below the mean of the Control group, increased significantly as one advanced from the ND/AE to the SE/AE to the FAS/PFAS group (χ^2 for trend: 4.8, $p = 0.03$) (Fig. 4*A*).

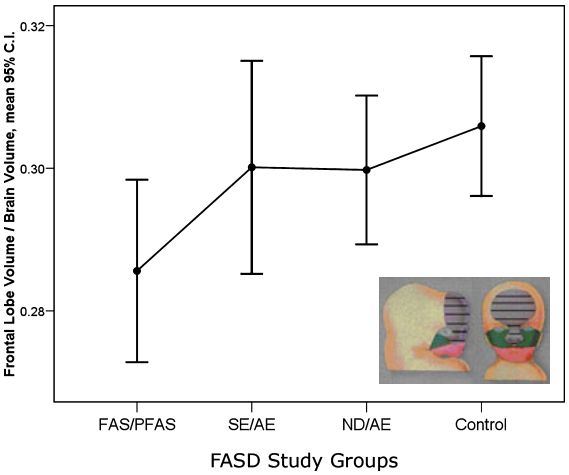

Fig. 3. The relative volume (cc) of the frontal lobe was significantly smaller in the fetal alcohol syndrome (FAS)/partial FAS (PFAS) group (after exclusion of the 2 subjects with agenesis of the corpus callosum/hypogenesis of the corpus callosum) compared with each of the other study groups. The FAS/PFAS group is the only group with the full FAS facial phenotype. Morphogenesis of the middle and upper face is heavily influenced by signals emanating from the forebrain to the frontonasal prominence (Marcucio et al., 2005). The frontonasal prominence is the striped region in the insert depicting a 5-week (left) and 10-week (right) fetus (Moore et al., 1994). C.I.: confidence interval; FASD, fetal alcohol spectrum disorders; SE, static encephalopathy; AE, alcohol exposed; ND, neurobehavioral disorder; FAS, fetal alcohol syndrome; PFAS, partial FAS.

Importantly, this demonstrated that even when the FAS facial phenotype was missing and the level of brain dysfunction was mild to moderate (4-Digit CNS Rank 2 in ND/AE group), there was a significant increased risk of underlying structural brain abnormality relative to the Control group (Fisher exact test, $p = 0.005$). Further evidence of structural brain abnormality along the full continuum of mild to severe brain dysfunction was observed by dividing the 81 subjects into 3 groups based on their 4-Digit CNS Rank: Rank 1 (no dysfunction), Rank 2 (mild to moderate dysfunction), and Rank 3 (severe dysfunction). The absolute size of all brain regions (with the exception of the CC, putamen, and CV) decreased significantly and incrementally progressing from CNS Rank 1 to 2 to 3. The only measures of the CC that decreased significantly with increasing CNS Rank were CC length and CC region 1 midsagittal area. Figure 4*B* serves to illustrate one of these findings, the significant decrease in the mean absolute volume of the caudate progressing from CNS Rank 1 to 2 to 3 (ANOVA overall $F = 13.5$; df: 2,77; $p < 0.001$: unweighted linear trend $F = 25.8$; df: 1,74; $p < 0.001$). The Duncan range test confirmed that all 3 mean caudate volumes were significantly distinct from one another.

Size of Brain Regions and Alcohol Exposure

Reported prenatal alcohol exposure patterns (frequency, quantity, and duration) across the 3 FASD study groups are

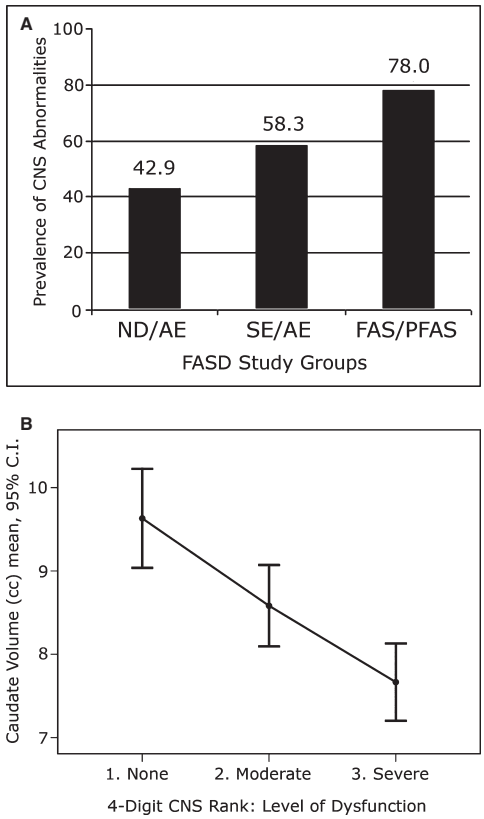

Fig. 4. (**A**) Prevalence of subjects in each FASD study group that had 1 or more brain regions, 2 or more SDs below the mean size observed in the Control group. (**B**) Mean absolute caudate volume decreased as a global measure of brain function (4-Digit Code CNS Rank) increased in impairment. C.I., confidence interval; FASD, fetal alcohol spectrum disorder; SE, static encephalopathy; AE, alcohol exposed; ND, neurobehavioral disorder; FAS, fetal alcohol syndrome; PFAS, partial FAS; CNS, central nervous system.

presented in detail in the neuropsychological/psychiatric report for this study (Astley et al., 2009b) and briefly in Table 1. Of the 65 subjects with FASD, 64 had confirmed prenatal alcohol exposure and one with full FAS had an unknown exposure. More detailed information on quantity, frequency, and/or trimester of alcohol use was available on 53 of the 65 alcohol-exposed subjects. The size of various brain regions decreased significantly and incrementally among the subjects with FASD with increasing frequency, quantity, and/or duration of reported alcohol exposure.

Days Per Week. Significant inverse correlations (Pearson Correlation Coefficients with p values < 0.05) were observed between the average number of days per week of drinking during pregnancy and the size of the following brain regions: midsagittal area of the brain (−0.306), absolute (−0.435) and relative (−0.306) volumes of the hippocampus, and CC length (−0.327).

Maximum Drinks Per Drinking Occasion. Significant inverse correlations were also observed between the maximum number of alcoholic drinks consumed per drinking occasion during pregnancy and the size of the following brain regions: relative volume of the frontal lobe (−0.430) (Fig. 5*A*), relative volume of the caudate (−0.373), and the absolute (−0.463) and relative (−0.538) volumes of the hippocampus.

Trimester of Exposure. A significant linear decrease in the mean relative volume of the frontal lobe was also observed when the FASD study sample was divided into groups based on their duration of exposure [exposure through first trimester only (n = 10, mean: 0.31, SD: 0.03); through the second trimester only (n = 9, mean: 0.29, SD: 0.02); and through all 3 trimesters (n = 32, mean: 0.28, SD: 0.02); ANOVA overall F = 3.1; df: 2,50; p = 0.05; unweighted linear trend, F = 6.1; df: 1,50; p = 0.017] (Fig. 5*B*). Post hoc comparison tests confirmed that the mean relative volume of the frontal lobe was significantly smaller among those with 3 trimesters of exposure relative to those with exposure through just the first trimester. Interestingly, the mean relative volume of the frontal lobe of the unexposed Control group (mean: 0.31, SD: 0.02, n = 16) was comparable with the 2 FASD groups with exposure through the first and second trimesters, but was significantly larger than the group with exposure through all 3 trimesters.

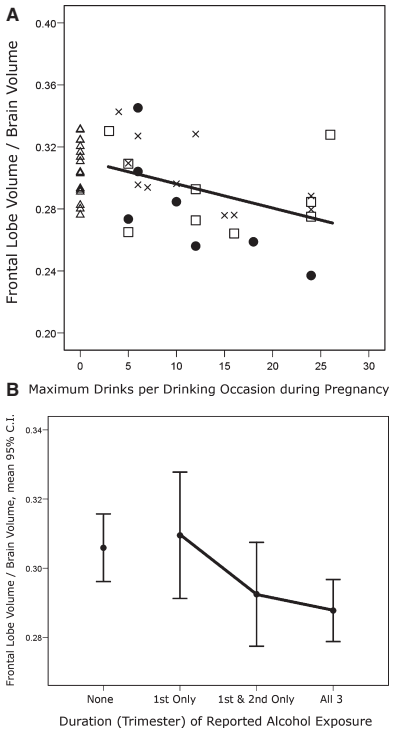

Fig. 5. (**A**) The relative volume of the frontal lobe decreased significantly with increasing maximum number of alcohol drinks per drinking occasion during pregnancy among subjects with FASD (Pearson Correlation Coefficient −0.430, $p < 0.02$). (**B**) A significant linear decrease in the mean relative volume of the frontal lobe was also observed when the FASD study sample was divided into groups based on their duration of exposure (exposure through first trimester only, n = 10, mean: 0.31, SD: 0.03; through the second trimester only, n = 9, mean: 0.29, SD: 0.02; and through all 3 trimesters, n = 32, mean, 0.28, SD: 0.02) (ANOVA overall F = 3.1; df: 2,50; p = 0.05; unweighted linear trend, F = 6.1; df: 1,50; p = 0.017). The unexposed Control group is plotted for visual comparison. C.I., confidence interval; FASD, fetal alcohol spectrum disorder. Circle = FAS/PFAS, square = SE/AE, X = ND/AE, triangle = control.

DISCUSSION

Overall, all 3 primary hypotheses were supported in this study. *Hypothesis 1:* progressing across the 4 study groups from Controls to ND/AE to SE/AE to FAS/PFAS, the mean absolute size of most brain regions decreased significantly in size. The frontal lobe and caudate were disproportionately reduced in size. *Hypothesis 2:* even though the FAS/PFAS and SE/AE groups had comparably severe levels of brain dysfunction (CNS Rank 3), those with the FAS facial phenotype had significantly smaller frontal lobes, frontal lobe gray matter volume, and CV. *Hypothesis 3:* the risk of underlying structural abnormalities increased linearly as one advanced from ND/AE to SE/AE to FAS/PFAS, relative to Controls. Most notably, 43% of subjects in the ND/AE group had 1 or more brain regions that were 2 or more SDs below the mean of the Control group, despite only mild to moderate brain dysfunction, no FAS facial phenotype, and the absence of microcephaly. MRI provided further validation that ND/AE, SE/AE, and FAS/PFAS, as defined by the FASD 4-Digit Code, are 3 clinically distinct and increasingly more affected diagnostic subclassifications under the umbrella of FASD. The significant inverse correlations between quantity, frequency, and timing of alcohol exposure and size of selected brain regions provided further evidence of a potential causal association between alcohol exposure and structural brain abnormality observed in this study population. It is important to note that the findings reported in this study are reflective of the 4-Digit Code definitions used to generate the FASD study groups. While all FASD diagnostic systems (Astley, 2004; Bertrand et al., 2004; Chudley et al., 2005; Hoyme et al., 2005) share some common clinical terminology (e.g., FAS and PFAS), the criteria used to define these diagnostic classifications are not the same.

FASD Diagnostic Classification Systems

When comparing outcomes across published FASD MRI studies, it is important to note that not all investigations use the same FASD diagnostic criteria to establish their FASD study groups. In many fields, readers of research data can draw their own conclusions about the comparability of diagnostic subgroups because the diagnostic criteria are widely established, or in newer fields of study, the diagnostic methods would be presented in sufficient detail. At present the FASD MRI literature lacks the diagnostic detail necessary

when a field has not yet settled on common diagnostic standards. Most FASD MRI studies to date have classified their subjects into 1 or more of the following groups: (i) an alcohol-exposed group with FAS facial features (FAS), (ii) an alcohol-exposed group without FAS facial features (e.g., ARND or FAE); or (iii) a group in which all FASD subgroups are combined into 1 group with PEA. Criteria used to define FAS groups are typically described qualitatively (e.g., known prenatal alcohol exposure, craniofacial anomalies consistent with FAS, prenatal or postnatal growth deficiency or both, and CNS dysfunction). Criteria used to define ARND groups are also described qualitatively (e.g., exposed to high levels of alcohol but display few or none of the facial features characteristic of FAS, and do not show growth retardation). But these qualitative descriptions do not adequately convey what goes into the classifications of FAS, ARND, or FAE. Missing are parameters such as what level of growth deficiency must be present, what level of CNS dysfunction must be present, which FAS facial features must be evident, and how severe the facial anomalies had to be. Without this information, it is not clear if clinically distinct study groups have been established or how they are clinically distinct. Nor can it be determined if the FAS/FASD group in 1 study is comparable with the FAS/FASD group in another study. As the field has matured, there is now clear consensus that more rigorous diagnostic methods should be used and several more rigorous methods have been published (Astley, 2004; Bertrand et al., 2004; Chudley et al., 2005). Two groups of investigators (Astley and Clarren, 2000; Hoyme et al., 2005) have demonstrated in 2 large clinical populations that the majority (50–87%) of FAS diagnoses rendered using gestalt diagnostic methods did not meet FAS criteria when more rigorous diagnostic criteria were applied.

To help bridge the gap between the different diagnostic terms used in the FASD literature, our ND/AE and SE/AE groups would be most comparable with mild and severe ARND, respectively. Our FAS/PFAS group will differ from other groups labeled FAS or PFAS if the diagnostic criteria used to establish the groups differ. Our FAS/PFAS, SE/AE, and NE/AE groups span the entire continuum of FASD. The effort here is to describe groups across the full fetal alcohol spectrum and to retain sufficient statistical power to detect clinically meaningful differences between diagnostic subgroups. Combining possible subtypes into 1 larger alcohol-exposed group may obscure actual differences between these subtypes. In the current study, most neuroimaging differences would not have been revealed if the 3 FASD study groups had been combined in any way and compared with the Controls. We suggest the following questions as standards for review and interpretation of current and future literature on neuroimaging and behavioral outcomes in FASD: (i) What diagnostic criteria are used to establish the study groups? (ii) Has the magnitude of growth deficiency, FAS facial features, CNS structural/functional abnormality, and alcohol exposure been reported to confirm that study groups are clinically distinct? (iii) When significant differences between groups are not observed, does the study have clinically distinct groups and sufficient sample size/power to support null findings? and (iv) When outcomes between FAS groups differ between studies, is this because outcomes differ or the definition of FAS differs?

MRI FASD Literature

In general, the FASD MRI literature documents significant reductions in the size of many but not all brain regions studied, when comparing full FAS to a healthy control group. The current study supports and extends these findings. The FASD MRI literature also documents marginal effects in PEA, FAE, or ARND groups relative to FAS or healthy controls, but these differences are rarely statistically significant. The current study provides definitive evidence that when these nondysmorphic FASD clinical subgroups are more rigorously defined and subdivided (e.g., SE/AE and ND/AE) (Astley, 2004), significant differences are observed not only when each of these FASD groups is compared with a healthy control group, but also when each is compared with the other. These findings provide compelling evidence that clinically meaningful and distinct subgroups do exist under the umbrella of FASD, and at least 2 distinct subgroups exist under the broad classification ARND (e.g., SE/AE and ND/AE). Key outcomes in the current study are discussed below and compared with the FASD MRI literature, with emphasis on findings specific to FASD clinical subgroups and how subgroups are clinically defined.

Total Brain. In the current study, total brain size became incrementally smaller progressing across the 4 study groups from Control to FAS/PFAS. This was influenced, in part, by the criteria used to construct the 4 groups. Microcephaly is a sufficient but not necessary CNS criterion for diagnosis of FAS, PFAS, and static encephalopathy/alcohol-exposed subjects. Of note, however, is the finding that the prevalence of microcephaly was fourfold greater in the FAS/PFAS group relative to the SE/AE group. Both groups were required to meet the same criteria for CNS damage/dysfunction (CNS Rank 3 and/or 4). The only difference between the criteria for the 2 groups was that the FAS/PFAS group had to have FAS facial features (Face Ranks 3 or 4) and SE/AE group had to have normal facial features (Face Ranks 1 and 2). Thus, the fact that microcephaly was far more prevalent in the group with the FAS facial features is a further evidence that 4-Digit Code definition of the FAS face is a marker for underlying structural abnormality. The impact of alcohol on reduction of overall brain size is well documented in the animal and human FASD literature (Archibald et al., 2001; Hoyme et al., 2005; Mattson and Riley, 1995; Sowell et al., 2001b; Stratton et al., 1996). The current study provided definitive evidence of the continuum of effects across the full spectrum, not just among those with FAS.

Frontal Lobe. The most notable and novel finding in the current study was a significant reduction in absolute and relative volume of the frontal lobe in the FAS/PFAS relative to all other groups including the SE/AE group. The significant difference observed between FAS/PFAS and SE/AE indicates individuals with FASD and the FAS facial features have smaller frontal lobes than those with FASD, but no facial features, despite the fact that both groups had comparably severe cognitive/behavioral impairment (4-Digit CNS Rank 3: 3 or more domains of function, 2 or more SDs below the mean) (Astley et al., 2009b). Archibald and colleagues (2001) using a study sample of 14 FAS and 12 PEA by gestalt diagnosis and 41 controls and Sowell and colleagues (2001b) using a subset of the Archibald study sample, 14 FAS and 7 PEA by gestalt diagnosis and 21 controls, were unable to detect significant differences in absolute or relative measures of frontal lobe volumes between FAS, PEA, and controls. Further analysis of the Sowell and colleagues (2001b) study population (Sowell et al., 2002a) using surface-based image analysis revealed a significant reduction in the absolute volume and a significant increase in the relative volume of the frontal lobe, when the 14 FAS and 7 PEA were combined and compared with 21 controls. Wass and colleagues (2001) reported significant reductions in the absolute size of the frontal cortex associated with prenatal alcohol exposure in an ultrasonographic study of 167 pregnant women. The percent of fetuses with a frontal cortex below the 10th percentile increased from 4% for nonexposed fetuses to 23% for heavily exposed fetuses.

Frontal Lobe Gray–White Matter. Although we observed significantly smaller absolute volumes of white matter and gray matter in the frontal lobes among subjects with FAS/PFAS relative to Controls, the proportion of the frontal lobe that contained white matter did not vary significantly across the 4 study groups. These findings are consistent with the literature. Archibald and colleagues (2001) identified a significant proportional reduction of white matter across the entire cerebrum among subjects with a gestalt diagnosis of FAS relative to Controls. When their analysis was repeated for each lobe (frontal, parietal, temporal, and occipital), a significant proportional reduction of white matter was only observed in the parietal lobe. When subsets of these children were further assessed by Sowell and colleagues (2001b, 2002a) proportional reductions in white matter were observed in the left hemisphere perisylvian cortices of the temporal and parietal lobes (not in the frontal lobes) among alcohol-exposed subjects relative to Controls.

Caudate. The caudate, lenticular nuclei, some subthalamic nuclei, and the substantia nigra are subcortical gray matter structures that form the basal ganglia (Cote and Crutcher, 1990). The caudate nucleus has extensive neural connections to the frontal lobes and is thought to mediate higher cognitive and executive function. Like the frontal lobe, the absolute and relative volume of the caudate was significantly reduced in the current study but unlike the frontal lobe this reduction in size was observed in both the FAS/PFAS and SE/AE groups relative to the Control group. Archibald and colleagues (2001) reported that the absolute and relative size of the caudate was significantly reduced in 14 children with a gestalt diagnosis of FAS relative to 41 controls. But no significant caudate reductions were observed among their group of 12 children with PEA. Cortese and colleagues (2006) assessed caudate size in an fMRI study with a very small sample of children (7 with FAS and 4 with FAE by gestalt diagnosis, and 4 controls). They reported significantly smaller absolute, but not relative, caudate volumes in the FAS group relative to controls, but the unconventional use of one-tailed p values increased the probability of achieving statistical significance. No caudate differences were detected between their FAE and control groups. It is noteworthy that no significant differences in intracranial volume were detected between their FAS, FAE, and control groups.

Putamen. The putamen (part of the lenticular nuclei) together with the caudate form the striatum. The putamen is innervated by neurons from the primary motor, premotor, supplementary motor, and somotosensory cortices, whereas the caudate receives input from frontal eye fields and association areas of the frontal and parietal lobes (Cote and Crutcher, 1990; Giedd et al., 1994). In the present study, the absolute but not relative volume of the putamen was significantly smaller in the FAS/PFAS group relative to the SE/AE, ND/AE, and Control groups. Mattson and colleagues (1996) in a study of 6 children with FAS (by gestalt diagnosis) reported that the absolute but not relative volume of the lenticular nuclei was significantly smaller relative to 7 controls. Archibald and colleagues (2001) reported no significant absolute or relative reduction in the size of the lenticular nucleus among 14 FAS or 12 PEA (by gestalt diagnosis) when compared with 41 controls.

Hippocampus. The hippocampus is a structure of the limbic system involved in learning, memory storage, and retrieval (Eichenbaum et al., 1992). In the present study, the mean absolute volume of the hippocampus decreased significantly, progressing across the 4 study groups from Control to FAS/PFAS. In contrast, Archibald and colleagues (2001) reported a disproportionate sparing of the hippocampus in an otherwise hypoplastic brain among 14 FAS participants (by gestalt diagnosis) relative to 41 controls.

Corpus callosum. The CC is a large bundle of nerve fibers connecting the 2 hemispheres of the brain. CC deficits have been linked to deficits including intellectual functioning, learning, memory, executive function, and attention. In this study, the absolute midsagittal area of the genu (Region 1) and the length of the CC were comparably small across the FASD groups and significantly smaller relative to the Control group. No significant differences were observed after adjustment for midsagittal brain area. Riley and colleagues

(1995) reported significant decreases in the absolute midsagittal area of the CC and regions 1, 3, 4, and 5 among 11 alcohol-exposed subjects (9 with FAS by gestalt diagnosis) relative to 12 controls. After adjustment for midsaggital brain area, regions 1 (genu), 4, and 5 (splenium) remained significantly smaller but overall midsagittal area did not. The more severe outcomes reported by Riley and his colleagues were not due to differences in diagnostic methodology, as our outcomes reflected our entire alcohol-exposed group. It does appear the alcohol-exposed group in the study by Riley and colleagues was more severely impaired than our alcohol-exposed group. They had a substantially lower FSIQ and were drawn from a sample with a higher estimated prevalence of ACC (3/44 or 6.8%). In a more recent study, Sowell and colleagues (2001a) observed the size, shape, and location of the CC among 20 alcohol-exposed subjects (13 with FAS by gestalt diagnosis) and 21 controls. Again, in contrast to our findings, they reported significant reductions in the absolute midsagittal area of the CC and all 5 subregions in their alcohol-exposed group relative to their control group. Their more severe findings could be explained by the much higher prevalence of microcephaly in their alcohol-exposed population (they report "most" were microcephalic). Only 18% of our alcohol-exposed group was microcephalic. After adjustment for brain volume, only the splenium in their alcohol-exposed group remained significantly smaller. Their key finding was a significant anterior-inferior displacement of the splenium in the alcohol-exposed relative to controls. Based on their published Figs. 2 and 3 illustrating this effect, this finding would appear to be commensurate to our finding of a shorter CC. Autti-Ramo (2000) reported that CC was significantly shorter (7.4%), the midsagittal area significantly smaller (13.8%), and the width of the splenium significantly smaller (12%) among 17 alcohol-exposed subjects (5 with FAS by gestalt diagnosis) relative to 17 controls. These differences were no longer significant after adjustment for midsagittal area of the brain. Forty-one percent of their alcohol-exposed population was microcephalic. Bookstein and colleagues (2002a,b) reported a variety of shape but not size differences in the CC of subjects with gestalt diagnoses of FASD versus controls. It is important to remember that brain regions are inherently highly variable in shape and size, even in typically developing individuals (Steen et al., 2007). This is clearly evident in our Control population. They present with extraordinary variability in CC shape (Fig. 2*C*) despite their high level of cognitive function and absence of alcohol exposure. One final comparison with the literature is warranted. Miller and colleagues (1999) reported that the absolute size of the CC was significantly larger in ethanol-exposed nonhuman primates relative to unexposed controls. The number of axons (not the axon size or myelin thickness) was significantly greater, especially in the rostral half of the CC (anterior to where the fornix joins the CC). It is important to note that total brain volume was comparable between the exposed and unexposed groups, no animal had microcephaly, and the alcohol-exposed animals had mild to moderate cognitive dysfunction with possibly only 1 animal having full FAS. Several human studies, including ours, have reported sparing of some anterior callosal regions in their alcohol-exposed group. We observed a significant relative sparing of CC Region 2. Riley and colleagues (1995) observed significant absolute and relative sparing of CC Region 2 and Sowell and colleagues (2001a) reported relative but not absolute sparing of anterior callosal regions.

What appears to be 1 recurring theme across several FASD studies is that the CC is reduced in length and the regions most impacted are the genu and splenium. These findings are consistent with the developmental spectrum of ACC. CC abnormalities are present in a multitude of syndromes and disease entities (Paul et al., 2007). ACC is not specific to prenatal alcohol exposure. ACC is present in 2 to 3 per 100 individuals with general developmental disability (Jeret et al., 1986). The CC is the major commissure forming a junction between the cerebral hemispheres. The formation of the CC starts with the development of the genu in week 11; the body, isthmus and splenium develop at a later stage through week 20 of gestation (Paul et al., 2007). If the normal developmental process is disturbed, the CC may be absent completely or partially ("hypogenetic"). As the developmental process starts from the anterior part and progresses from front to rear, when the CC is hypogenetic, it is usually the posterior portion that is affected the most (the posterior body and the splenium) (Fig. 2*B*).

Cerebellar vermis. The cerebellum is located at the base of the brain and is involved in motor, cognitive, and affective functions (Vidal et al., 2006). The absolute but not the relative midsagittal area of the CV and lobules I–V were significantly smaller in the FAS/PFAS group relative to the Controls and SE/AE in the current study. Sowell and colleagues (1996) reported a significant reduction in the absolute midsagittal area of lobules I–V in a group of alcohol-exposed subjects (6 FAS and 3 PEA by gestalt diagnosis) relative to 24 controls. They did not report if these findings remained significant when adjusted for overall brain size. More recently, O'Hare and colleagues (2005) reported significant reductions in the midsagittal area of lobules I–V and the VIII–X in a group of alcohol-exposed subjects (14 FAS and 7 PEA by gestalt diagnosis) relative to 21 controls. After correction for brain size, lobule I–V remained significantly reduced in size. Goodlett and colleagues (1990), using an animal model, demonstrated that the number of Purkinje cells was significantly reduced in earlier maturing regions of the CV (lobules I–V and VIII–X) after a single critical day of neonatal alcohol exposure. Notably, the Purkinje cells in the later maturing neocerebellar vermis (lobules VI and VII) were apparently spared.

Prevalence of CNS Structural Abnormalities Among FASD Clinical Subgroups

From a FASD diagnostic perspective, it is interesting to note how many subjects within all 3 FASD clinical subgroups

had 1 or more brain regions, 2 or more SDs below the mean of the Control group. Although we reported the prevalence of anomalies in our FASD study groups using our research control group as the reference, this would not be an appropriate practice in a clinical setting. Norms for the size of brain regions adjusted for gender and age must be established using large, representative, population-based samples, rather than small, convenient research control samples. The National Institutes of Health (NIH) MRI Study of Normal Brain Development (Waber et al., 2007) is a landmark study that is documenting structural brain development and behavior longitudinally from birth to young adulthood in a large population-based sample of healthy children targeted to the United States 2000 census distribution.

Validation of the FASD 4-Digit Diagnostic Code

This study further validated (Astley and Clarren, 1996, 2000, 2001; Astley et al., 2002) the measurement scales and procedures for diagnostic classification used in the FASD 4-Digit Diagnostic Code. Statistically significant differences in neuropsychological outcomes (Astley et al., 2009b) and measures of brain structure were observed between the FAS/PFAS, SE/AE, and ND/AE groups, confirming that these groups reflect 3 clinically distinct and increasingly more affected diagnostic subclassifications under the umbrella of FASD. The prevalence/severity of structural brain abnormality increased significantly as dysfunction increased from CNS Rank 1 (no dysfunction) to Rank 2 (mild to moderate dysfunction) to Rank 3 (severe dysfunction). Indeed, when these CNS Ranks were first defined 10 years ago (Astley and Clarren, 2000), the underlying principle was that as the magnitude and breadth of functional impairment increased, the probability of underlying structural abnormality would increase. It is for this reason that the 4-Digit CNS Ranks 1, 2, and 3 were labeled "unlikely," "possible," and "probable" underlying CNS abnormality, respectively (Fig. 1). The finding that the subjects in the FAS/PFAS group with the 4-Digit FAS facial phenotype had significantly smaller frontal lobes than the SE/AE group with no FAS facial phenotype provides the most compelling data yet that this facial phenotype truly is a marker for underlying brain abnormality (Fig. 3). Several animal and clinical studies have documented correlations between midline facial anomalies and underlying brain abnormality caused by prenatal alcohol exposure (Astley and Clarren, 1996, 2001; Johnston, 1975; Sulik, 2005; Sulik and Johnston, 1982; Sulik et al., 1981, 1984). Morphogenesis of the middle and upper face is heavily influenced by signals emanating from the forebrain. Marcucio and colleagues (2005) report that a role of Sonic hedgehog (Shh) in the forebrain is to regulate Shh expression in the face, and that together, these Shh domains mediate patterning within the frontonasal prominence (Fig. 3) and proximodistal outgrowth of the middle and upper face.

The primary limitation of this study is the presence of other prenatal and/or postnatal risk factors, in addition to alcohol, that are capable of adversely impacting brain development. Clinical records for this FASD study sample documented that up to 83% of the mothers reportedly smoked during pregnancy, up to 67% reportedly used illicit drugs during pregnancy, and over 75% of the children were in foster/adoptive care (Astley et al., 2009b). While the significant dose–response associations observed between alcohol exposure and neurostructural alterations in this study provided compelling evidence of alcohol's potential causal role, one cannot rule out the impact of the other risk factors.

In conclusion, the results of this study confirm that significant differences in the sizes of many brain regions exist between children with FASD and their healthy peers. More importantly, when the FASD 4-Digit Code is used to create clinically distinct diagnostic subgroups under the umbrella of FASD (FAS/PFAS, SE/AE, and ND/AE), statistically significant differences in neurostructure are identified between the FASD diagnostic subgroups. Structural abnormalities were prevalent across the full spectrum of FASD. MRI could importantly augment the diagnosis of FASD, once population-based norms for structural development of the human brain are established.

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MAGNETIC RESONANCE IMAGING

Magnetic resonance spectroscopy outcomes from a comprehensive magnetic resonance study of children with fetal alcohol spectrum disorders ☆

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Abstract

Magnetic resonance (MR) technology offers noninvasive methods for in vivo assessment of neuroabnormalities. A comprehensive neuropsychological/behavioral, MR imaging (MRI), MR spectroscopy (MRS) and functional MRI (fMRI) assessment was administered to children with fetal alcohol spectrum disorders (FASD) to determine whether global and/or focal abnormalities could be identified and to distinguish diagnostic subclassifications across the spectrum. The four study groups included (1) FAS/partial FAS; (2) static encephalopathy/alcohol exposed (SE/AE); (3) neurobehavioral disorder/alcohol exposed (ND/AE) as diagnosed with the FASD 4-Digit Code; and (4) healthy peers with no prenatal alcohol exposure. Results are presented in four separate reports: MRS (reported here) and neuropsychological/behavioral, MRI and fMRI outcomes (reported separately). MRS was used to compare neurometabolite concentrations [choline (Cho), *n*-acetyl-aspartate (NAA) and creatine (Cre)] in a white matter region and a hippocampal region between the four study groups. Choline concentration in the frontal/parietal white matter region, lateral to the midsection of the corpus callosum, was significantly lower in FAS/PFAS relative to all other study groups. Choline decreased significantly with decreasing frontal white matter volume and corpus callosum length. These outcomes suggest low choline concentrations may reflect white matter deficits among FAS/PFAS. Choline also decreased significantly with increasing severity of the 4-Digit FAS facial phenotype, increasing impairment in psychological performance and increasing alcohol exposure. NAA and Cre concentrations did not vary significantly. This study provides further evidence of the vulnerability of the cholinergic system in FASD.

Keywords: Fetal alcohol spectrum disorder (FASD); Magnetic resonance spectroscopy (MRS); FASD 4-Digit Diagnostic Code; Choline; *n*-Acetyl-aspartate; Creatine

1. Introduction

Fetal alcohol syndrome (FAS) is a permanent birth defect syndrome caused by maternal alcohol consumption during pregnancy. FAS is defined by growth deficiency, a unique cluster of minor facial anomalies and central nervous system (CNS) dysfunction and/or structural brain

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abnormalities [1]. The cognitive/behavioral problems in this condition stem from prenatal brain damage. Not all individuals with prenatal alcohol exposure present with measurable CNS dysfunction or structural brain abnormalities, and not all who present with measurable CNS dysfunction or structural brain abnormalities have FAS. Recently, the term *fetal alcohol spectrum disorders* (FASD) was coined to depict the spectrum of outcomes observed among individuals with prenatal alcohol exposure. FASD is not a medical diagnosis. Rather, medical diagnoses/conditions like FAS, Partial FAS, Static Encephalopathy/Alcohol Exposed and Neurobehavioral Disorder/Alcohol Exposed fall under the umbrella of FASD. The degree of brain damage among individuals with prenatal alcohol exposure may vary from microcellular and neurochemical aberrations to gross structural anomalies. Similarly, cognitive/behavioral dysfunction varies along the full continuum from mild developmental delay or learning disabilities to global developmental disability. The specificity of the FAS facial phenotype to prenatal alcohol exposure lends credence to the clinical judgment that the cognitive and behavioral dysfunction observed in individuals with FAS is due, at least in part, to brain damage caused by a teratogen [2-4]. Unfortunately, without the unique facial phenotype of FAS or at least a severe or clinically obvious expression of brain damage, the neurodevelopmental disabilities of an individual affected by prenatal alcohol exposure often go unrecognized and inappropriately served [5].

Many individuals with prenatal alcohol exposure exhibit cognitive difficulties and significant maladaptation that prevent them from leading productive, independent lives [6,7]. Across the population, the profile of cognitive dysfunction among individuals with prenatal alcohol exposure is highly variable, though there are some commonalities in functional compromise among subgroups, and conceptual models of overarching deficits have been proposed [8]. However, no single behavioral phenotype specific to alcohol teratogenicity has been described, and a single behavioral phenotype is unlikely. Without a behavioral phenotype specific to the teratogen alcohol, attributing an alcohol-exposed child's dysfunction to brain damage is often questionable at a clinical level [4]. If indisputable evidence of brain damage (e.g., alterations in neurostructure, neurometabolites and/or neuroactivation) could be found in these individuals, and linked to behavioral deficit, diagnostic efforts could be improved. The "disability" of these alcohol-exposed children would be clearly established and help facilitate eligibility for needed services. Furthermore, if specific alterations in neurostructure, neurometabolites and/or neuroactivation could be linked to clinically meaningful, discrete neuropsychological deficits, development of appropriate intervention programs could be accelerated.

The overall goal of this research study was to determine whether magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) and/or functional MRI (fMRI) could serve as noninvasive methods for definitively identifying global and/or focal brain abnormality across the full continuum of FASD and distinguish diagnostic subclassifications within the spectrum. The results of this comprehensive study are presented in four separate reports: MRS (presented here), and the neuropsychological/behavioral [9], MRI (submitted for publication) and fMRI [10] outcomes reported separately.

MRS measures concentrations of neurometabolites, including choline-containing compounds (Cho), markers of cell membrane stability and myelination; *N*-acetyl aspartate (NAA), a neuronal or axonal marker; and creatine (Cre), a marker of metabolic activity [11-14]. Decreased concentrations of Cho and/or NAA have been correlated with organic brain damage in many different disease states and disorders, and with varying levels of cognitive/behavioral dysfunction among both humans and animals [15-20]. Only three FASD MRS studies have been conducted to date, with varied outcomes [16,21,22]. The first FASD MRS study was conducted in a nonhuman primate model of FASD, back in the early 1990s [16]. Cho/Cre was measured in a 34×34×34-mm^3 region of interest that included the thalamus, parts of the internal capsule and basal ganglia, and adjacent white matter (Fig. 1A). Cho/Cre increased significantly with increasing duration of prenatal alcohol exposure and increasing impairment in neuropsychological function among animals with the human equivalent of alcohol-related neurodevelopmental disorder (ARND) (cognitive/behavioral impairment, but no physical stigmata of FAS). Interestingly, the only animal to deviate from this pattern was the animal with the most profound cognitive/behavioral impairment and the only live-born animal with FAS-like facial dysmorphia. Rather than having the highest Cho/Cre level, as would have been expected, this animal had the lowest Cho/Cre level (more than two standard deviations below the mean of all other study groups). It was speculated and reported at the time that this animal may have sustained a level of damage that was beyond that of the other animals, perhaps severe enough to result in depletion of cholinergic nuclei. Research in mice had previously confirmed that in utero ethanol exposure could cause severe depletion of cholinergic nuclei, with the most severe effects observed among those with FAS-like craniofacial anomalies [23]. NAA/Cre was also evaluated in the nonhuman primate study. Levels did not vary significantly with exposure or neuropsychological function. More recently, two FASD MRS studies have been conducted in humans, one focusing on the caudate nucleus [22], the other targeting several regions (parietal and frontal cortices, frontal white matter, corpus callosum, thalamus and cerebellar dentate nucleus) [21]. No significant Cho or Cho/Cre differences were observed between the FASD and control groups in either study. Cortese et al. [22] reported that NAA/Cre was significantly higher in their FASD group relative to their control group, whereas Fagerlund et al. [21] reported that NAA/Cre levels

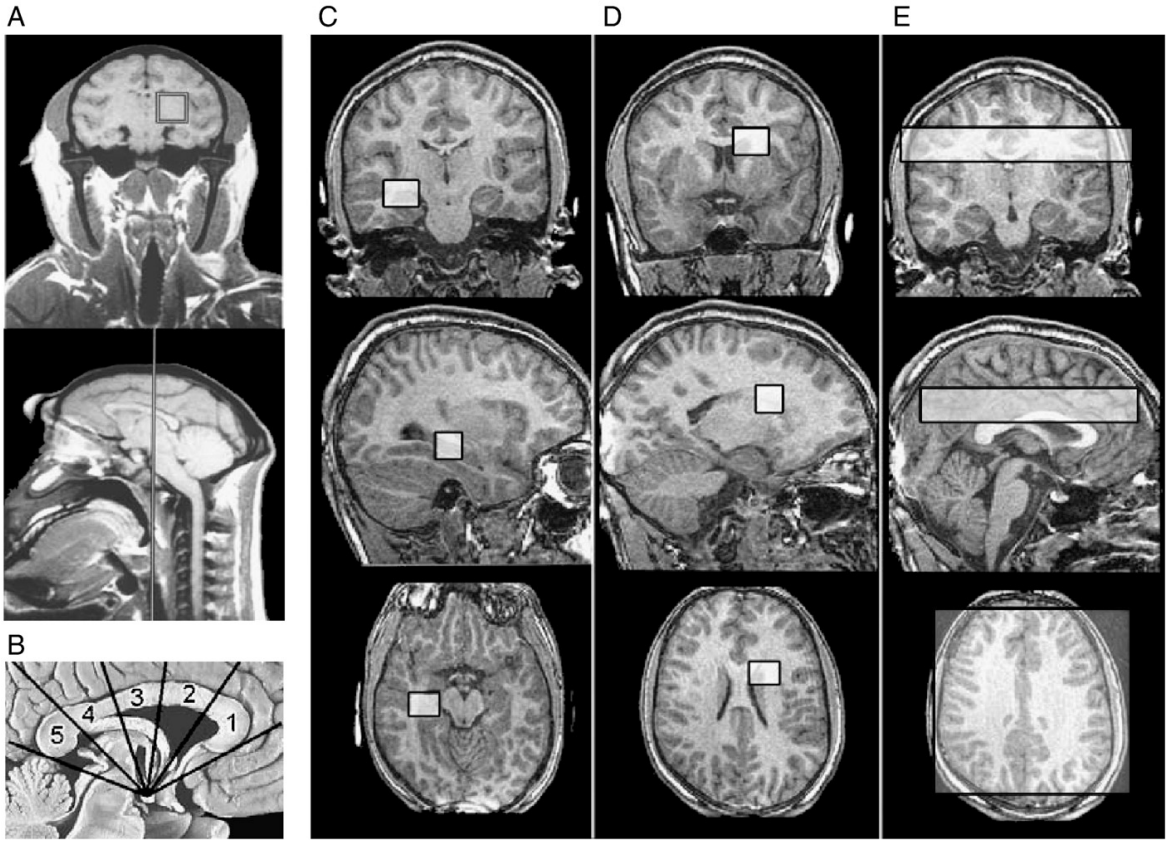

Fig. 1. Nonhuman primate FASD MRS study [16]. (A) The 34×34×34-mm^3 voxel included the thalamus, parts of the internal capsule and basal ganglia, and adjacent white matter. Current MRS Study. (B) Five equiangular subregions of the corpus callosum [(1) genu, (2) anterior body, (3) posterior body, (4) isthmus, (5) splenium] were constructed using the mammilary body as a point of reference. Coronal, sagittal and horizontal views of (C) 15×15×15-mm^3 hippocampus/basal nuclear voxel in the left hemisphere, (D) 15×15×15-mm^3 white matter voxel in the right frontal/parietal region (to replicate the voxel position in the previous nonhuman primate study) and (E) 20-mm-thick axial multivoxel slice (data to be presented in a separate report).

were significantly lower in their FASD group relative to their control group in parietal and frontal cortices, frontal white matter, corpus callosum, thalamus and cerebellar dentate nucleus.

The present study was conducted to assess absolute concentrations of Cho, NAA and Cre in two 15×15×15-mm^3 regions of interest: (1) a frontal/parietal white matter region, to replicate the region targeted in the nonhuman primate study [16]; and (2) a hippocampal/basal nuclear region, to extend the brain regions assessed in the human FASD MRS literature and overlap with a region assessed in the MRI component of this study.

2. Methods and materials

2.1. Subjects and study groups

The protocol was approved by the University of Washington Human Subjects Review Board. The three FASD groups were selected from among 1200 patients previously diagnosed by an interdisciplinary team in the WA State FAS Diagnostic & Prevention Network (FAS DPN) of clinics using the FASD 4-Digit Code [24,25]. Briefly, the four digits of the FASD 4-Digit Code reflect the magnitude of expression of the four key diagnostic features of FASD, in the following order: (1) growth deficiency, (2) characteristic FAS facial phenotype, (3) CNS structural/functional abnormalities and (4) prenatal alcohol exposure (Fig. 2). The magnitude of expression of each feature is ranked independently on a four-point Likert scale, with 1 reflecting complete absence of the FASD feature and 4 reflecting a strong "classic" presence of the FASD feature. Each Likert rank is specifically case defined. There are 256 possible four-digit diagnostic codes, ranging from 1111 to 4444. Each four-digit diagnostic code falls into one of 22 unique clinical diagnostic categories (labeled A through V). Seven of the 22 diagnostic categories (4-Digit Categories A–C and E–H) fall under the umbrella of FASD [(A) FAS/

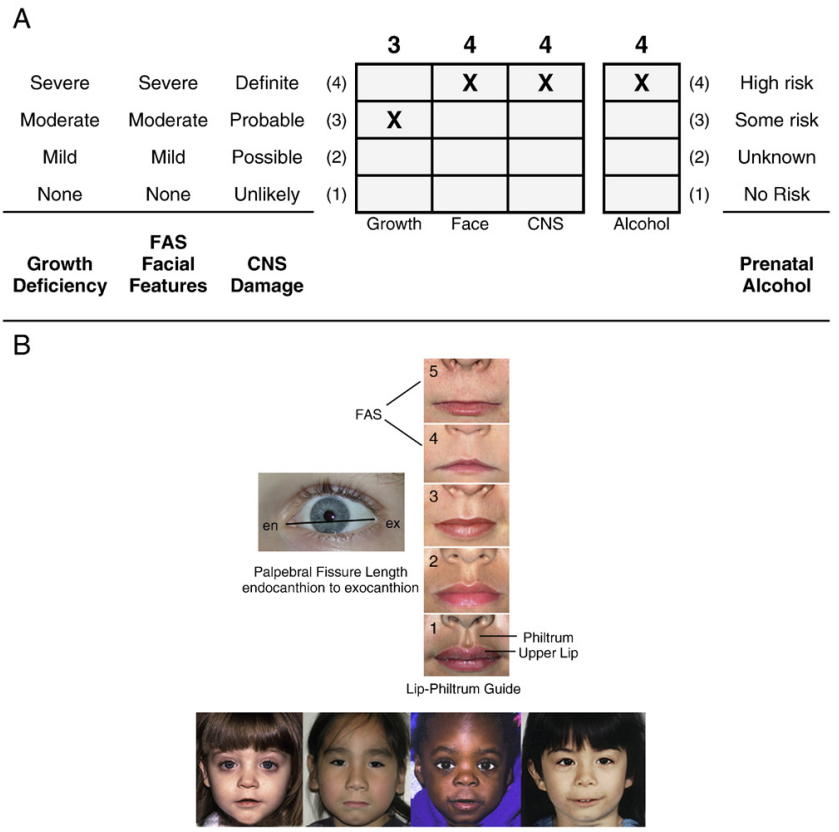

Fig. 2. (A) FASD 4-Digit Diagnostic Code. FASD is defined by growth deficiency, specific FAS facial features, evidence of CNS damage, and prenatal alcohol exposure. The 4-Digit Code ranks each of these areas on 4-point, case-defined, Likert scales. The 4-Digit Code (3444) inserted in the grid is 1 of 12 codes that meet the diagnostic criteria for FAS [25]. (B) The Rank 4 FAS facial phenotype, as defined by the FASD 4-Digit Diagnostic Code, requires the presence of all 3 of the following anomalies: (1) palpebral fissure length 2 or more standard deviations below the mean (2) smooth philtrum (Rank 4 or 5 on the Lip-Philtrum Guide); (3) thin upper lip (Rank 4 or 5 on the Lip-Philtrum Guide). Examples of the full Rank 4 FAS facial phenotype for Caucasian, Native American, African American, and Asian American children are shown (copyright Susan Astley Ph.D., University of Washington).

alcohol exposed, (B) FAS/alcohol exposure unknown, (C) partial FAS/alcohol exposed, (E–F) static encephalopathy/alcohol exposed and (G–H) neurobehavioral disorder/alcohol exposed]. The three FASD study groups in the current study represent these FASD diagnostic categories. This diagnostic system is currently being used by a wide variety of diagnostic teams in the USA and other countries. The control population was selected primarily from a large cohort of children enrolled at birth in a University of Washington study of typical development conducted through the Department of Speech and Hearing Sciences. With the enrollment of each child in the FAS/PFAS group, a child matched on age (within 6 months), gender and race was randomly identified and invited to enroll from the eligible SE/AE, ND/AE and control populations. The enrollment goal was 80 subjects (20 per group).

The study enrollment procedure produced a sample of 81 children of diverse ethnicity (Table 1). The age range (8 to 15.9 years) included the broadest age range of children that could be administered a comparable psychometric assessment battery and be reasonably capable of participating in the MR scanning. The 61 children with FASD were highly representative of the entire clinic sample of 1200 from which they were drawn. Each of the four study groups had 16–24 subjects successfully balanced on age, gender and race. The diagnostic features specific to each group were as follows:

1. Children in Group 1 had a four-digit diagnosis of *FAS or partial FAS (FAS/PFAS)* (e.g., 4-Digit Diagnostic Categories A–C: with Growth Ranks 1–4, Face Ranks 3–4, CNS Ranks 3 and/or 4, and Alcohol Ranks 2–4). Alcohol Rank 2 (unknown exposure) could only be present if the child had a diagnosis of full FAS because the Rank 4 FAS facial features are so specific to prenatal alcohol exposure [3,26]. Since the only clinical difference between FAS and PFAS in this study was the presence of growth deficiency in the former, FAS and PFAS were combined. In summary,

Table 1
Sociodemographic and 4-Digit Diagnostic Code profile of the four study groups. A more detailed profile with between-group analyses is presented in the neuropsychological/behavioral report for this study [9]

Characteristic		1. FAS/PFAS [a,b] (*n*=20)		2. SE/AE (*n*=24)		3. ND/AE (*n*=21)		4. Control (*n*=16)	
		n	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Gender	Female	10	(50.0)	8	(33.3)	10	(47.6)	8	(50.0)
Age at enrollment (years): mean (S.D.)		12.7	(2.4)	12.2	(2.0)	12.4	(2.3)	12.4	(2.7)
Race	Caucasian	12	(60.0)	11	(45.8)	12	(57.1)	13	(81.3)
4-Digit Code Ranks									
Growth rank	1. None	10	(50.0)	15	(62.5)	13	(61.8)	15	(93.7)
	2. Mild	2	(10.0)	2	(8.3)	6	(28.6)	1	(6.3)
	3. Moderate	5	(25.0)	3	(12.5)	1	(4.8)	0	(0.0)
	4. Severe	3	(15.0)	4	(16.7)	1	(4.8)	0	(0.0)
Face rank	1. None	0	(0.0)	4	(16.7)	7	(33.3)	10	(62.5)
	2. Mild	0	(0.0)	20	(83.3)	14	(66.7)	6	(37.5)
	3. Moderate	4	(20.0)	0	(0.0)	0	(0.0)	0	(0.0)
	4. Severe [c]	16	(80.0)	0	(0.0)	0	(0.0)	0	(0.0)
CNS Rank 1–3: Level of functional impairment	1. None	0	(0.0)	0	(0.0)	0	(0.0)	16	(100.0)
	2. Moderate	0	(0.0)	3 [d]	(12.5)	21	(100.0)	0	(0.0)
	3. Severe	20	(100.0)	21	(87.5)	0	(0.0)	0	(0.0)
CNS Rank 4: Structural/ neurologic abnormality	Present	13	(65.0)	6	(25.0)	0	(0.0)	0	(0.0)
Alcohol rank	1. No exposure	0	(0.0)	0	(0.0)	0	(0.0)	16	(100.0)
	2. Unknown exposure	1 [e]	(5.0)	0	(0.0)	0	(0.0)	0	(0.0)
	3. Confirmed exposure. Level moderate or unknown	7	(35.0)	12	(50.0)	11	(52.4)	0	(0.0)
	4. Confirmed exposure: Level high	12	(60.0)	12	(50.0)	10	(47.6)	0	(0.0)

[a] Six of the 20 subjects in Group 1 had full FAS using the 4-Digit Code. Ten of the 14 PFAS had Rank 4 Faces, but received a diagnosis of PFAS because of their absence of growth deficiency (Growth Rank 1).
[b] Two subjects had agenesis (PFAS) or hypogenesis (FAS) of the corpus callosum.
[c] Definition of Rank 4 FAS Face: palpebral fissure lengths 2 or more SDs below the norm, and lip and philtrum are Rank 4 or 5 on the Lip-Philtrum Guide [24].
[d] All three children with moderate functional impairment had structural evidence of brain abnormality (microcephaly).
[e] The one child with unknown prenatal alcohol exposure had full FAS.

children in Group 1 had severe cognitive/behavioral dysfunction and the FAS facial phenotype.

2. Children in Group 2 had a four-digit diagnosis of *static encephalopathy/alcohol exposed (SE/AE)* (e.g., 4-Digit Diagnostic Categories E and F: with Growth Ranks 1–4, Face Ranks 1–2, CNS Ranks 3 and/or 4, and Alcohol Ranks 3–4). In summary, children in Group 2 had severe cognitive/behavioral dysfunction, comparable to Group 1, but did not have the FAS facial phenotype.
3. Children in Group 3 had a four-digit diagnosis of *neurobehavioral disorder/alcohol exposed (ND/AE)* (e.g., 4-Digit Diagnostic Categories G and H: with Growth Ranks 1–4, Face Ranks 1–2, CNS Rank 2, and Alcohol Ranks 3–4). In summary, children in Group 3 had prenatal alcohol exposure comparable to Groups 1 and 2, but had only mild to moderate cognitive/behavioral dysfunction and did not have the FAS facial phenotype.
4. Children in Group 4 (*healthy controls/no alcohol exposure*) were selected based on parental report that the child was healthy, had no academic concerns and no prenatal alcohol exposure [e.g., 4-Digit Diagnostic Category V: with Growth Ranks 1–2, FAS Face Ranks (no restrictions), CNS Rank 1, Alcohol Rank 1]. In summary, these were nonexposed, healthy, average to high-functioning controls.

With the use of the FASD terminology introduced by the Stratton et al. [6], the SE/AE group most closely reflects 'severe ARND' and the ND/AE group reflects 'mild ARND'. A comprehensive analysis of the between-group differences of these diagnostic features is presented in the neuropsychological/behavioral report for this study [9].

2.2. Study participation

Participation in the study involved five visits over a 4- to 6-week study period. The neuropsychological and sociodemographic data were collected during Visits 1 and 2. The MR data were collected during Visits 3 and 4. Outcomes of the neuropsychological assessments were shared with the caregivers on Visit 5 and submitted to the child's medical record with caregiver consent.

2.3. Sociodemographic and clinical assessment

A comprehensive sociodemographic and health/medication history of each child was obtained by parent interview and record review. Information included birth data, growth,

and all prenatal and lifetime exposures and adverse events. For subjects with FASD, most information was obtained at the time of their FASD diagnostic evaluation. All controls had a reported absence of prenatal alcohol exposure. All children had a standardized digital facial photograph taken at the time of enrollment. The facial photographs were analyzed using the FAS Facial Analysis Software [27] to document the magnitude of expression of the FAS facial phenotype [26]. A more detailed methodology and analysis of the socio-demographic and FASD diagnostic outcomes, including prenatal alcohol exposure histories, are presented in the neuropsychological/behavioral report from this study [9].

2.4. Neuropsychological and psychiatric assessments

A detailed description of the assessment battery and a comprehensive analysis of the between-group differences in neuropsychological outcome are presented in the neuropsychological/behavioral report for this study [9]. Briefly, a comprehensive, standardized assessment battery was administered to each child/caregiver by a psychologist masked to group assignment. The assessment battery was designed to capture the domains of potential neuropsychological impairment seen as the result of the typically diffuse brain damage arising from alcohol teratogenesis (e.g., deficits in executive functioning, visual–spatial skills, learning, memory, academic achievement, speech/language and attention) [8,28-32]. The neuropsychological/behavioral outcomes served to profile the study groups and confirm the groups were clinically and statistically distinct from one another; fundamental to the interpretation of the MR outcomes.

2.5. MR Scanner

All scans (MRI, MRS and fMRI) were acquired using a General Electric 1.5-T scanner in the Diagnostic Imaging Sciences Center at the University of Washington.

2.6. MRI and fMRI

The MRI and fMRI [12] components of this study are reported separately. Briefly, MRI was used to measure the size of the following brain regions: total brain, frontal lobe, caudate, putamen, hippocampus, corpus callosum and cerebellar vermis. fMRI was used to assess neuroactivation in selected brain regions during performance of N-back working memory tasks.

2.7. MR Spectroscopy

The MRS protocol included both single-voxel and multivoxel proton echo planar spectroscopic imaging (Fig. 1C–E). Both of these techniques were included because there are parts of the brain (axial slice at the level of the thalamus) which allow for multivoxel spectroscopy and there are parts of the brain (hippocampus) that best scan with single-voxel techniques due to magnetic field susceptibility problems near the base of the brain. Metabolite concentrations including Cho, NAA and Cre were obtained in absolute concentrations from the single-voxel spectroscopy and relative concentrations (Cho/Cre and NAA/Cre) from the multivoxel spectroscopy. Due to the vast amount of data acquired in the MRS component of this study, this report will focus on the single-voxel spectroscopic imaging. The multivoxel methodology and outcomes will be summarized in a separate, future publication.

2.7.1. Single voxel

Single-voxel MR spectroscopy targeted two 15×15×15-mm^3 regions of interest: a right frontal/parietal white matter region and a left hippocampus/basal nuclear region (Fig. 1C and D). The *hippocampus voxel* targeted the left hippocampus, but due to the size of the voxel, a portion of the left basal nuclear region was also included. The *white matter voxel* was predominated by white matter superior to the caudate and lateral to Regions 2 and 3 of the corpus callosum. Due to the size of the voxel, the superior tip of the caudate was included. The exact position of the MRS single voxel in three dimensions was overlayed on top of the 3D anatomical image for coregistration purposes to define the extent of tissue overlap as shown in Fig. 1C and D. Point-resolved-spectroscopy pulse sequence and the proton brain exam technique developed by General Electric [33] were used. This technique allows the MR technician to choose the location and size of the volume of interest and then fully automates the adjustment of (1) RF transmit power; (2) center frequency; (3) magnetic field homogeneity; (4) water suppression pulses parameters; and (5) phasing and display of the proton spectra. The 15×15×15-mm^3 voxels were positioned over the left hippocampal region and the right frontal/parietal white matter region. Data was then acquired using the following parameters: FID size 2048 complex points; spectral width 2000 Hz; spectral frequency of 63.8 MHz; TR/TE 2000/30 ms. The MRS signal was averaged 128 times so the total acquisition time was 4 min and 16 s. A water spectrum of the same region was also acquired (without water suppression) for quantification used in the LC model software. To optimize the LCModel parameters, phantoms with known concentrations of brain metabolites were prepared and scanned at various acquisition settings. From these spectra, libraries of phantom data, or basis sets, were created as detailed in the LCModel manual [34]. The MR signal strength from the metabolites scanned in the phantoms were used to calculate brain tissue concentrations. The absolute concentrations (millimoles) of Cho, NAA and Cre were computed as detailed in the LCModel manual [34,35] consistent with other techniques employing water referencing [36,37]. Following line fitting, both metabolites and water amplitudes were adjusted for acquisition parameters (receiver settings and transmitter gain) and voxel size compared to the phantom data. Water amplitudes were then adjusted using estimates of water molarity and attenuation [36] and multiplied by the tissue fraction within the voxel. Dividing adjusted metabolite peak amplitudes by this

corrected water term yielded metabolite concentrations. Tissue fraction was calculated by summing the CSF voxels within the larger MRS voxel which were segmented out using the high-resolution 3D anatomical image and then dividing the brain volume (total volume−CSF volume) by the total MRS voxel volume. In other words, this software does a correction for the MRS signal attenuation caused by CSF volume based on each individual high-resolution anatomical scan. Quantification of Cho, Cre and NAA required an additional step to correct metabolite data for the differential T2 of the phantom data compared to typical in vivo estimates [34]; this step served to scale concentration output similar to our previous work [37,38]. The ratios Cho/Cre and NAA/Cre were also assessed for comparison to a previous nonhuman primate FASD MRS study [16]. Throughout this report, these metabolites will be preceded by the letter 'h' or 'w' to reflect whether they were derived from the hippocampus or white matter voxels.

2.8. MRS Hypotheses

In this report, the analyses focus on neurometabolite differences between the four study groups. The hypotheses were derived from the previous nonhuman primate FASD MRS study [16], the human FASD MRS literature [21] and confirmation from the neuropsychological/behavioral [9] and MRI components of this study that the four study groups present along a continuum of increasing impairment.

2.8.1. Primary hypotheses

1. The mean Cho concentration (and/or Cho/Cre) in the white matter and/or hippocampus voxels will be lower in the FAS/PFAS group than in the control, ND/AE and SE/AE groups [16].
2. The mean Cho concentration and/or Cho/Cre in the white matter and/or hippocampus voxels will be higher in the functionally impaired but nondysmorphic alcohol-exposed groups (SE/AE and ND/AE) relative to the control group [16].
3. The mean NAA concentrations and/or NAA/Cre in the white matter and/or hippocampus voxels will decrease as one advances across the four study groups from controls to ND/AE to SE/AE to FAS/PFAS [21].

2.8.2. Secondary exploratory hypotheses

1. Cho and/or NAA concentrations in the hippocampal and/or white matter voxels will correlate with alterations in size of brain regions measured in the MRI component of this study.
2. Cho and/or NAA concentrations will correlate with prenatal alcohol exposure (quantity, frequency, timing) [16].

2.9. Statistical analysis

The statistical analyses used to confirm the four study groups were effectively balanced on age, gender and race as described in Part I of this study [9].

2.9.1. Primary hypotheses

Multivariate ANOVA was used to determine whether differences in mean metabolite concentrations existed among the study groups. If significant differences existed, the Duncan post hoc range test was used to identify which group means differed. The Duncan test makes pairwise comparisons using a stepwise procedure. Means were ordered from highest to lowest, and extreme differences were tested first. The Duncan test sets a protection level for the error rate for the collection of tests and identifies homogeneous subsets of means that are not different from one another at the P=.05 level. Age, gender and race were assessed as potential covariates. An a priori test for linear trend was included in the ANOVA to determine whether the mean concentration of Cho, Cho/Cre, NAA and/or NAA/Cre increased or decreased as one advanced across the study groups as specified in the hypotheses. Two-tailed P values of .05 were used throughout the analyses.

2.9.2. Secondary hypotheses

The objective of the secondary analyses was to test additional a priori hypotheses that further supported and extended the primary hypotheses. Due to the increased risk of type I errors resulting from multiple comparisons, all secondary analyses should be considered exploratory and P values interpreted accordingly. These secondary analyses take advantage of a rich dataset and generate hypotheses for future studies. Pearson correlation coefficients were used to assess the strength and direction of an association between two variables measured on continuous scales. ANOVA was used to compare means between groups. Chi-square tests were used to compare proportions between two or more groups.

2.9.3. Power/sample size

This study had 80% power or greater to detect the following effect sizes at a two-tailed alpha level of 0.05: (1) a difference in means equal to or greater than the standard deviation of the mean difference; (2) a correlation coefficient of 0.30 or greater; and (3) a 35-point or greater difference in proportions between two groups. Brooks et al. [37] demonstrated that changes in metabolite concentrations (NAA, Cre, Cho) as small as 12% could be confidently discerned when rigorous positioning guidelines and automated spectral fitting for measuring the cerebral metabolites were used.

3. Results

3.1. Metabolite concentrations across the four study groups: (primary hypotheses)

Metabolite concentrations did not vary by age, race, or gender in this study population.

3.1.1. Choline: white matter voxel

The mean absolute wCho concentration in the frontal/parietal white matter voxel, situated in the right hemisphere, was significantly lower (7% to 12% lower) in the FAS/PFAS

group relative to each of the other study groups (Table 2, Fig. 3A). No significant linear trends were observed across the study groups.

3.1.2. Choline: hippocampus voxel

The mean absolute hCho concentration in the hippocampus voxel was on average 7% to 8% lower in the FAS/PFAS group relative to each of the other study groups (Table 2). These differences were not statistically significant. The mean, absolute hCho concentration was 8% lower in the FAS/PFAS group relative to all other groups combined (mean 1.41, S.D. 0.21) (Table 2, Fig. 3B). This difference was near significant (t=−1.8, P=.07). No significant linear trends were observed across the study groups.

3.1.3. NAA: White matter and hippocampus voxels

The mean absolute NAA concentrations in the white matter and hippocampus voxels were on average 2% to 6% lower in the FAS/PFAS group relative to the control group, but no significant differences or linear trends were observed across the study groups (Table 2).

3.1.4. Cre: White matter and hippocampus voxels

No significant group differences or linear trends across the groups were observed in the mean absolute Cre concentrations in the white matter or hippocampus voxels (Table 2).

3.1.5. Cho/Cre: White matter and hippocampus voxels

The Cho/Cre ratios followed the same pattern as the absolute measures of Cho, but the magnitudes of the differences were slightly smaller and the variability of the differences slightly greater (Table 2). The mean Cho/Cre ratios in the white matter and hippocampus voxels were lower in the FAS/PFAS group relative to each of the other groups, but the overall ANOVAs were not statistically significant. Although it is customary not to conduct post hoc pairwise contrasts when the overall ANOVA is not significant, it is important to report from an exploratory standpoint that the mean Cho/Cre level was 9% lower in the FAS/PFAS group relative to the control group in both the white matter (t=2.0, P=.058) and hippocampus (t=1.9, P=.061) voxels. In addition, the mean hCho/Cre in the hippocampus voxel was significantly lower in the FAS/PFAS group than in the other three groups combined (mean 0.26, S.D. 0.03) (t=2.1, P=.041). The lower hCho/Cre ratios in the FAS/PFAS group appeared to be driven by low hCho, not by high hCre. No significant linear trends were observed across the groups.

3.1.6. NAA/Cre: White matter and hippocampus voxels

No significant group differences or linear trends across the groups were observed in mean NAA/Cre in the white matter or hippocampus voxels (Table 2).

Table 2
MRS Study group: metabolite concentrations in the white matter and hippocampus single voxels across the four study groups

Metabolite: single-voxel location	Group								Statistics				
	1. FAS/PFAS (n=20)		2. SE/AE (n=24)		3. ND/AE (n=21)		4. Control (n=16)		ANOVA				
									Overall		Post hoc Duncan	A priori linear trend[a]	
	Concentration (mM)		Concentration (mM)		Concentration (mM)		Concentration (mM)		F[b]	P	Homologous groups	F[c]	P
	Mean	(S.D.)	Mean	(S.D.)	Mean	(S.D.)	Mean	(S.D.)					
Cho													
White matter	1.24	(.17)	1.37	(.19)	1.32	(.19)	1.39	(.14)	2.7	(.05)	1, 234	0.04	(.84)
Hippocampus	1.31	(.23)	1.42	(.21)	1.40	(.25)	1.42	(.17)	1.1	(.36)		0.01	(.92)
NAA													
White matter	8.10	(1.00)	8.45	(1.09)	8.48	(1.23)	8.31	(1.15)	0.5	(.66)		0.30	(.56)
Hippocampus	6.89	(.94)	7.22	(1.07)	6.95	(1.33)	7.33	(.98)	0.7	(.58)		0.80	(.38)
Cre													
White matter	5.47	(.57)	5.73	(.67)	5.75	(.72)	5.60	(.88)	0.7	(.55)		0.30	(.59)
Hippocampus	5.34	(.69)	5.43	(.78)	5.33	(.69)	5.32	(.59)	0.1	(.96)		0.04	(.84)
Cho/Cre													
White matter	.229	(.033)	.242	(.046)	.233	(.041)	.251	(.032)	1.1	(.35)		0.40	(.53)
Hippocampus	.246	(.033)	.263	(.039)	.262	(.029)	.270	(.037)	1.5	(.22)		0.30	(.61)
NAA/Cre													
White matter	1.48	(.16)	1.49	(.26)	1.48	(.13)	1.49	(.17)	0.03	(.95)		0.01	(.93)
Hippocampus	1.30	(.19)	1.35	(.25)	1.31	(.23)	1.39	(.21)	0.5	(.67)		0.80	(.36)

Duncan: The Duncan multiple comparison range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at P<.05. F: F-statistic. Linear trend: ANOVA unweighted linear trend across the four study groups. N/A: Not applicable.

[a] Linear trends involving Cho and Cho/Cre were assessed across three groups (control, ND/AE, SE/AE). All other linear trends were assessed across all four groups.

[b] Numerator degrees of freedom (df)=3; denominator df=total sample size minus 4.

[c] Numerator df=1; denominator df=total sample size minus number of groups.

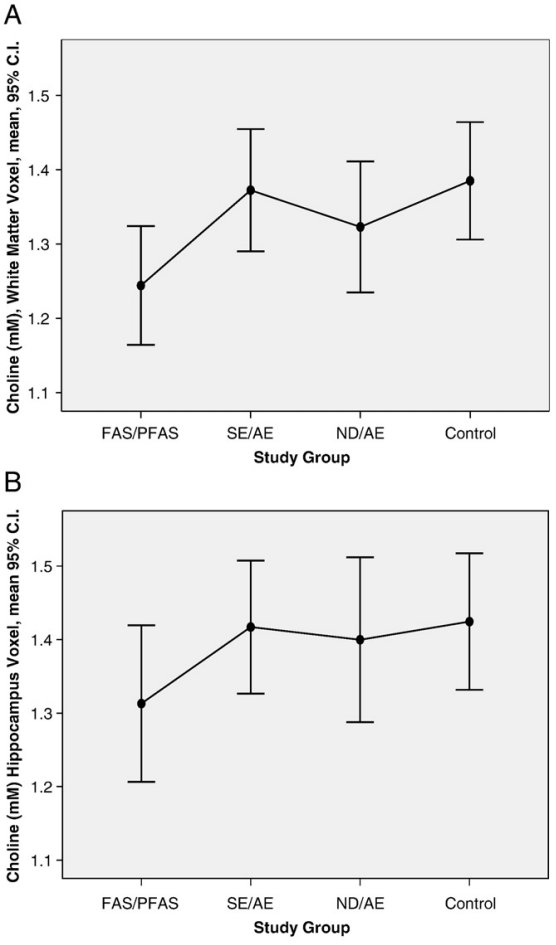

Fig. 3. Choline concentration (millimolar) across all the four study groups in the (A) frontal/parietal white matter and (B) hippocampus voxels.

3.2. Correlation between brain structure and metabolite concentrations (Secondary Hypothesis 1)

Significant differences in the sizes of brain regions between the four study groups were observed in the MRI component of this study. Correlations between metabolite concentrations and the size of brain regions assessed by MRI are presented in Table 3.

3.2.1. White matter voxel

The 15×15×15-mm^3 voxel in the right hemisphere included the superior tip of the caudate, but was predominated by white matter in the frontal/parietal region, lateral to Regions 2 and 3 of the corpus callosum (Fig. 1B). The wCho concentration decreased significantly with decreasing volume of the frontal lobe white matter and the midsagittal area of cerebellar vermis lobules 1–5. wCho also decreased significantly with decreasing midsagittal area of the corpus callosum as a whole and of each of its five subsections (most strongly with Region 3). wCho concentration was not significantly correlated with total brain volume. The wNAA concentration in the white matter voxel, situated lateral to Regions 2 and 3 of the corpus callosum, decreased significantly with decreasing midsagittal area of Region 3 of the corpus callosum.

3.2.2. Hippocampus voxel

The hCho concentration in the voxel that included the hippocampus and basal nuclear region in the left hemisphere decreased significantly with decreasing size of the left hippocampus, frontal lobe, corpus callosum, cerebellar vermis lobules 6–7, putamen and total brain (Table 3). hNAA, hCre, hNAA/Cre and hCho/Cre levels in the hippocampus voxel did not correlate significantly with the size of any brain region.

3.2.2.1. Partial voluming. It is important to note that a fixed-size voxel will capture more surrounding tissue in a smaller brain than in a larger brain. This is referred to as partial voluming. This could influence the mean metabolite concentration within a voxel, since metabolite concentrations vary normally by region and tissue type. The mean total volume of the brain for the FAS/PFAS group was 11% smaller than that for the control group. Thus, the fixed-size voxel in the hippocampal region would capture, on average, 11% more surrounding tissue in the FAS/PFAS group than in the control group. The mean hCho concentration in the FAS/PFAS group was 1.31 mM compared to 1.42 mM in the control group. If the lower hCho level in the FAS/PFAS group was solely an artifact of inclusion of 11% more tissue from adjoining regions, those adjoining regions would have to have exceptionally low hCho levels (0.32 mM or lower, if one assumes the remaining 89% of the voxel had a mean hCho level of 1.42 like the controls) to reduce the mean hCho level in the FAS/PFAS hippocampus voxel to 1.31. This magnitude of variation in Cho concentration between adjacent tissues far exceeds the normal regional variation reported in the literature [39,40]. Due to the size of the voxel placed in the hippocampus region, hippocampal and basal nuclear regions were captured in all subjects, including those in the control group (Fig. 1C). It would appear from visual inspection of the hippocampus voxel that inclusion of adjacent tissue would likely increase the white matter content of the voxel. Cho levels are typically higher in white matter than in gray matter [39-41]. If the FAS/PFAS voxel had a higher proportion of white matter, one would expect the hCho level in the hippocampus voxel in the FAS/PFAS group to be higher than that in the control group, not lower. The FAS/PFAS group was not the only group with microcephaly. Two subjects in the SE/AE group had microcephaly. The mean hCho concentrations in the two subjects with microcephaly were identical to the mean hCho level in the remaining subjects with normocephaly in

Table 3
MRS-MRI: Pearson correlation coefficients between the size of brain regions and absolute Cho and NAA concentrations in the left hippocampus and right white matter voxels

Brain structure	Choline concentration (mM)		NAA Concentration (mM)	
	Left hippocampus voxel hCho	Right white matter voxel wCho	Left hippocampus voxel hNAA	Right white matter voxel bNAA
Total brain volume (cm^3)	.270**	.134	.042	.187
Total brain midsagittal area (cm^2)	.188	.200	.166	.142
Frontal lobe volume (cm^3)	.320**	.208	.028	.159
Frontal lobe gray matter volume (cm^3)	.287**	.151	.095	.126
Frontal lobe white matter volume (cm^3)	.298**	.263*	−.42	.203
Corpus callosum				
Midsagittal area (cm^2)	.280**	.448**	.141	.162
Length (cm)	.258*	.363**	.036	.104
Region 1: genu midsagittal area (cm^2)	.145	.310**	.052	.125
Region 2: midsagittal area (cm^2)	.071	.263**	.074	.147
Region 3: midsagittal area (cm^2)	.245*	.379**	.028	.208*
Region 4: midsagittal area (cm^2)	.257*	.257*	.063	.071
Region 5: splenium midsagittal area (cm^2)	.189	.373**	.006	.071
Cerebellar vermis				
Midsagittal area (cm^2)	.197	.197	−.043	.097
Lobules 1–5: midsagittal area (cm^2)	.114	.277**	−.121	.112
Lobules 6–7: midsagittal area (cm^2)	.307**	.075	.075	.033
Lobules 8–10: midsagittal area (cm^2)	−.028	.144	−.104	.102
Right caudate volume (cm^3)	.079	−.019	−.078	.130
Left caudate volume (cm^3)	.005	−.027	−.067	−.008
Total caudate volume (cm^3)	.041	−.023	−.073	.059
Right putamen volume (cm^3)	.285**	.193	.011	.136
Left putamen volume (cm^3)	.169	.135	.047	−.054
Total putamen volume (cm^3)	.243*	.175	.030	.046
Right hippocampus volume (cm^3)	.077	.195	.049	.137
Left hippocampus volume (cm^3)	.220*	.155	.124	.082
Total hippocampus volume (cm^3)	.154	.180	.090	.112

* $P<.05$.
** $P<.01$.

the SE/AE group. Thus, inclusion of adjacent tissue in the hippocampus voxel of these two subjects did not result in a lower hCho level. These results suggest, but do not confirm, that the lower hCho among the FAS/PFAS group is not solely an artifact of partial voluming.

3.3. Alcohol and metabolite concentrations (Secondary Hypothesis 2)

Differences in prenatal alcohol exposure histories between the four study groups are presented in Part I [9]. Although all three FASD groups had comparably high levels of exposure, the proportion of subjects with exposure in all three trimesters increased significantly as one advanced across the four groups from controls to FAS/PFAS. Several measures of prenatal alcohol exposure (quantity, frequency, timing) correlated with metabolite concentrations. For example, the wCho decreased significantly with increasing number of days per week of drinking reported just prior to pregnancy (Pearson correlation coefficient −.300, P=.031, n=52). Of the 53 alcohol-exposed subjects with documented exposure by trimester, 11 were reportedly exposed only in the first trimester, 9 only through the second trimester and 33 through all three trimesters. The mean wCho concentration was identical between the 16 controls (mean 1.39, S.D. 0.14) and the nine subjects with first trimester-only exposure (mean 1.39, S.D. 0.18) (Fig. 4). The mean wCho concentration was significantly lower among the 42 subjects with exposure through the second or third trimesters (mean 1.29, S.D. 0.18) than the 26 subjects with no exposure or exposure only through the first trimester (mean 1.39, S.D. 0.15) (t=2.1, P=.48). A near-significant correlation was observed between hCho and alcohol exposure when average number of days of drinking was multiplied by average number of drinks per occasion just prior to pregnancy (Pearson correlation coefficient −.281, P=.07, n=41). No significant correlations were observed between alcohol exposure and NAA or Cre concentrations in either the hippocampus or white matter voxels.

4. Discussion and conclusions

4.1. Primary MRS findings

The primary findings of this study include the following.

4.1.1. Frontal/parietal white matter voxel

A significant decrease (7–12%) was observed in the wCho concentration in the FAS/PFAS group relative to each of the other study groups. wCho in the frontal/parietal white matter voxel also decreased significantly with decreasing

Fig. 4. The mean Cho concentration (millimolar) in the frontal/parietal white matter voxel was significantly lower among the 46 subjects with alcohol exposure through the second and third trimesters than the 26 subjects with no exposure or exposure only through the first trimester.

corpus callosum size, frontal lobe white matter volume and increasing level of alcohol exposure. The wNAA concentration also decreased with decreasing size of corpus callosum region 3. The white matter voxel was aligned lateral to corpus callosum regions 2 and 3.

4.1.2. Hippocampus voxel

A near significant 8% decrease was also observed in the hCho concentration in the FAS/PFAS group relative to all other groups combined. The hCho concentration in the left hippocampus voxel decreased significantly with decreasing size of several brain regions, most notably the left hippocampus and the frontal lobe. The frontal lobe is innervated by cholinergic projections from the nucleus basilis of Meynert (basal nucleus) [42]. Both the basal nucleus and hippocampus were captured in the hippocampus voxel.

4.2. What do the Cho, NAA and Cre metabolite levels reflect?

4.2.1. NAA (A neuronal or axonal marker)

NAA is an amino acid found only in neurons and is synthesized in the brain. The –CH3 group of NAA is visible as a large narrow peak at 2.02 ppm in ^{1}H spectra obtained from human brain [14] (Fig. 5). The quantity of NAA varies regionally; some studies demonstrate it increases rostrally [41]. NAA is an indicator of neuronal development/degradation [43]. Reduced cranial NAA has been associated with axonal loss, active degradation of NAA, injured neurons, gliosis and/or dysfunctional or inhibited mitochondria.

4.2.2. Cre (A marker of metabolic activity)

The creatine signal, constituted of both creatine and phosphocreatine, reflects energy phosphate metabolism [13]. The Cre peak was thought to be relatively constant between individuals and in most brain areas [36]; therefore, it was often used as an internal reference. However, the accuracy of Cre as an internal standard is controversial, because Cre can vary under pathological conditions [44]. Cre is found in greater concentrations in gray matter than in white matter [45].

4.2.3. Cho (A marker of cell membrane integrity, myelination)

Cho is a precursor of two important molecules: phophatidylcholine (PtdCho) and acetylcholine (ACho). Cho is present in membranes of all cells, where it constitutes the polar subunit of PtdCho (i.e., lecithin), sphingomyelin and plasmalogens. Within cholinergic neurons, Cho is also the precursor for the synthesis of the neurotransmitter ACho [46]. The rate of ACho synthesis is regulated by the concentration of substrate Cho in cholinergic neurons. ACho is a neurotransmitter that is critical for many aspects of memory, cognition and mood [47]. The Cho peak at 3.22 ppm includes phosphorylcholine, glycerophosphocholine and a relatively negligible amount of free choline [14]. Phosphorylcholine and glycerophosphocholine constitute the precursors and degradation products of PtdCho. Thus, the Cho signal reflects the precursors and degradation products of PtdCho, not PtdCho itself. PtdCho is the membrane-bound form of Cho. An increase in the Cho peak is associated with an increase in membrane breakdown or turnover, myelination or inflammation, and has been observed in demyelinating diseases [48] and in brain tumors [49,50]. The major phospholipids in brain membranes are PtdCho, phosphatidylserine (PtdS) and phosphatidylethanolamine (PtdE). The phosphatides account for 85% of total brain phospholipids. Moreover, the choline in PtdCho represents about 80% of the total membrane-bound choline in the brain. PtdCho is a cellular phospholipid reservoir that

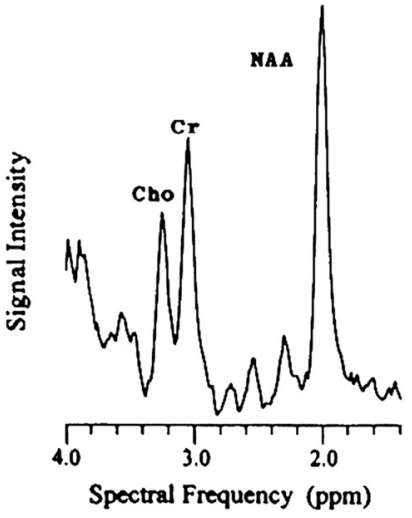

Fig. 5. Spectral frequency showing key metabolites: Cho, Cre and NAA.

provides free choline for ACho synthesis. When free extracellular Cho is absent, stimulated cells experience a decrease in PtdCho, PtdE and PtdS in the membranes. Addition of extracellular Cho protects the membranes from declines in PtdCho, PtdE and PtdS. The protective effect of exogenous Cho on the stimulus-induced depletion of membrane phosphatides depends on its concentration [51].

4.3. Regional variation of Cho, NAA and Cre in healthy individuals

Metabolite concentrations vary between white and gray matter tissue and between different regions of the brain in healthy individuals [39-41]. Wiederman et al. [41] reported that NAA in frontal gray matter is 15% lower than in frontal white matter and 14% lower than in parietal gray matter. Cho in frontal gray matter is 41% lower than in frontal white matter and 25% greater than in parietal gray matter. Cho in parietal gray matter is 53% lower than in parietal white matter. Cre in parietal gray matter is 13% higher than in parietal white matter. Deganonkar et al. [52] and Soher et al. [53] both found that Cho concentrations were higher in the genu than in the splenium of the corpus callosum of normal subjects. The cause of these regional variations is unclear, but it presumably reflects the cellular composition of the different brain regions, with glial cells believed to have higher Cho levels than neuronal cell types [54,55]. Their results were consistent with those of Pouwels and Frahm [40] who demonstrated an anterior–posterior concentration gradient in Cho along the midline, with the highest value in the frontal region among normal subjects.

4.4. Comparison to the nonhuman primate FASD MRS study

Consistent with the nonhuman primate FASD-MRS study [16], only the group with FAS/PFAS had significantly low wCho. In contrast to the nonhuman primate FASD MRS study, significant increases in Cho/Cre with increasing duration of alcohol exposure or functional impairment were not observed across the nondysmorphic control, ND/AE and SE/AE groups. It is important to note that advancements in design and technology afforded greater precision and accuracy in the current study. Although the scans from both studies were obtained in the same scanner and the white matter voxels were placed in the same region, advanced technology allowed the current voxel to be one-third the size of the voxel used in the primate study, and the absolute concentration of Cho (rather than the concentration relative to Cre) could now be accurately obtained. Most importantly, the human study included more severely affected individuals (20 with FAS/PFAS). The primate study had only one animal with facial dysmorphia and cognitive impairments consistent with the human equivalent of FAS. The remaining alcohol-exposed primates had outcomes commensurate with the SE/AE and ND/AE groups. No animal had microcephaly. In the primate study, it was speculated that the increased Cho/Cre signal in the primates may have been associated with membrane breakdown, based on the mechanism of cholinergic membrane vulnerability postulated by Wurtman et al. [56]. Wurtman et al. [56] hypothesized that Cho-deprived cholinergic neurons catabolize their own membranes to free up Cho for acetylcholine synthesis. They suggested that this dual use of Cho for membrane and neurotransmitter synthesis could make acetylcholine-producing cells particularly vulnerable to alterations in Cho levels. If acetylcholine was deficient, as has been reported in several animal models of in utero alcohol exposure [57], breakdown of cholinergic neuron membranes could serve as a compensatory measure to free up Cho for acetylcholine synthesis. If cholinergic membranes were breaking down, one would expect to observe elevated Cho/Cre signals. The only animal that deviated from the pattern of increased Cho/Cre with increasing cognitive/behavioral impairment was the one animal with FAS. That animal had the lowest Cho/Cre. It was speculated at the time that that animal may have sustained a level of damage that was beyond that of the other animals, perhaps severe enough to result in depletion of cholinergic nuclei. In such case, compensatory measures such as membrane breakdown would be less successful in achieving adequate acetylcholine levels and would result in a lower Cho/Cre signal. Schambra et al. [23] confirmed that in utero ethanol exposure can cause severe depletion of cholinergic nuclei. In the mildly affected brains of fetal mice, fewer cells were immunoreactive for CAT in the medial septal nucleus and diagonal band of Broca. In the severely affected brains, cells immunoreactive to CAT were totally absent. The severely affected mice had craniofacial anomalies consistent with those in humans with FAS and the single primate with 'FAS'. Schambra et al. [23] reported that without the projection of the cholinergic neurons of the medal septal nucleus and diagonal band of Broca to the hippocampus, hypoplasia of the hippocampus occurs and memory deficits as well as difficulty inhibiting unwanted behaviors could be expected, as is typically reported in FASD. As presented below, this is consistent with what was observed in the current study.

4.5. wCho concentration, frontal white matter volume and corpus callosum length

The volume of white matter in the frontal lobe and the length of the corpus callosum were significantly smaller in the FAS/PFAS group relative to all other groups (Fig. 6B and C). wCho in the voxel located in the right frontal/parietal white matter, lateral to Regions 2 and 3 of the corpus callosum, was also significantly lower in the FAS/PFAS group relative to all other groups (Fig. 6A). wCho levels decreased significantly with decreasing corpus callosum length and frontal white matter volume across all four study groups (Fig. 6D–F). And wNAA (a purported measure of neuronal or axon density) decreased with decreasing size of corpus callosum region 3. These findings suggest the decreased wCho levels among FAS/

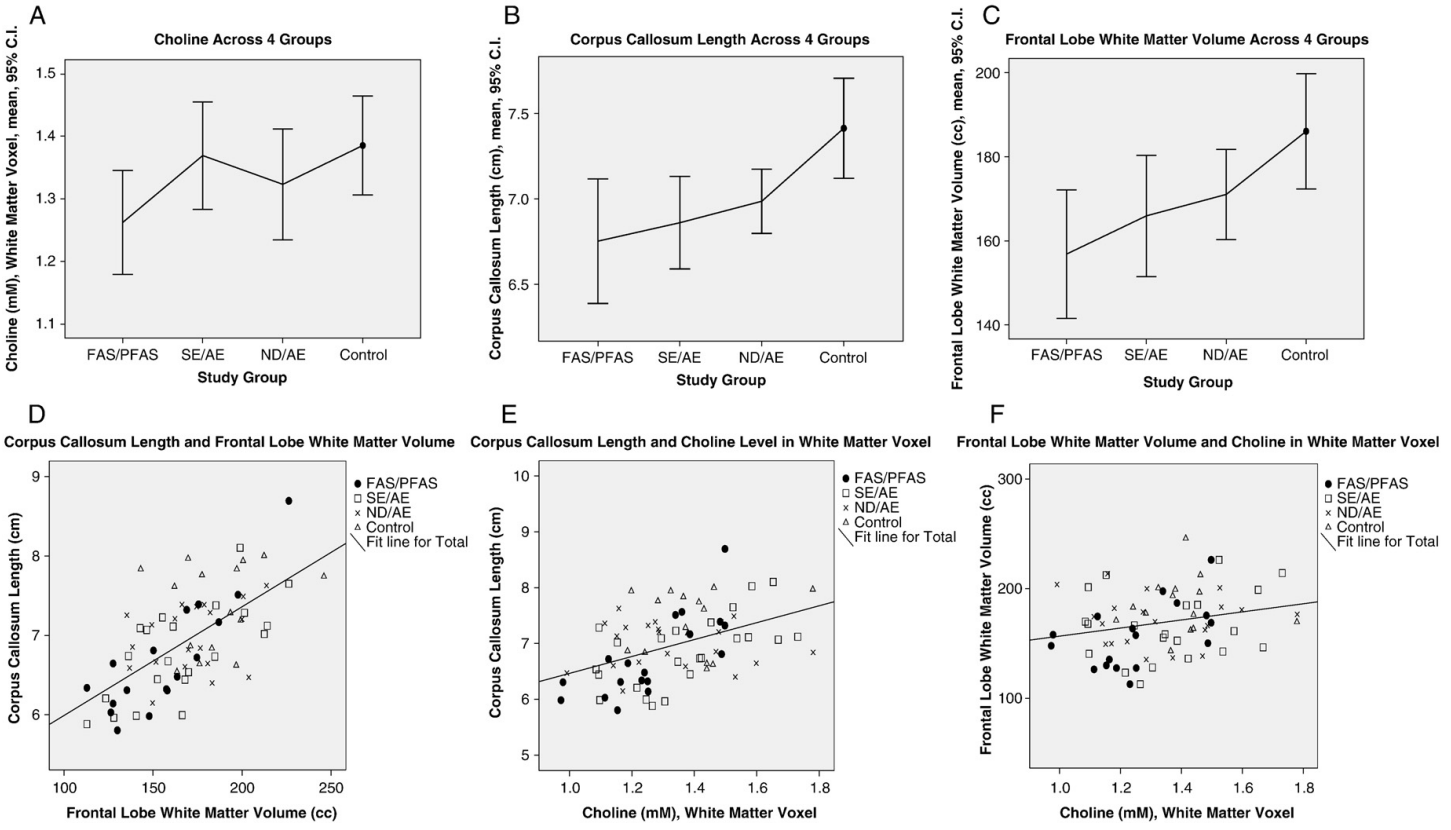

Fig. 6. The FAS/PFAS group had (A) significantly lower wCho concentration in the white matter voxel, (B) shorter corpus callosum lengths and (C) smaller frontal lobe volumes than controls. (D) The smaller the frontal lobe, the shorter the corpus callosum (Pearson correlation coefficient 0.64; $P<.001$). (E) The shorter the corpus callosum, the lower the wCho concentration (Pearson correlation coefficient 0.45; $P<.001$). (F) The smaller the frontal lobe, the lower the wCho concentration (Pearson correlation coefficient 0.24; $P=.04$). Four study groups: FAS/Partial FAS, SE/AE; ND/AE; healthy control with no alcohol exposure.

PFAS in this study may be reflective of white matter deficits among FAS/PFAS. Studies of the regional distribution of Cho in the normal brain show that Cho concentrations are higher in white matter than in gray matter due to the multiple phospholipid layers of myelin [40]. The main metabolites that contribute to the proton-detected Cho resonance in vivo are phosphocholine and glycerophosphocholine. These compounds are involved in the metabolism of the membrane lipids phosphatidylcholine (i.e., lecithin) and certain amidephosphocholines (i.e., sphingomyelin). Due to its high myelin content, white matter contains more lipids than gray matter (15.6% vs. 5.9% of total wet weight) and also shows a different lipid composition. Under normal physiologic conditions, both lecithin and sphingomyelin are subject to continuous breakdown and resynthesis. Cho concentrations in older children (5–18 years) are about 15% below the levels in infants and young children (0–5 years) [58]. This difference has been attributed to the fact that myelination during early childhood causes a pronounced turnover of membrane precursor molecules. Although there is also a continuous turnover of myelin in adults, the initial process of myelination requires a considerably larger amount of phosphocholine, which is both a key substrate for the glycerophospholipids in myelin and a major contributor to the proton MRS-detected Cho resonance.

Volumetric neuroimaging studies in FASD have also shown that white matter structures have suffered larger losses than gray matter structures [20,59,60]. High-resolution 3D MRI and whole-brain surface-based image analysis procedures [60] have shown increased gray matter density and decreased white matter density bilaterally in posterior temporal and inferior parietal regions in alcohol-exposed subjects, suggestive of abnormal myelination. Myelin is made of the membranous processes from glial cells that wrap themselves around axons [61]. Animal studies have shown that astroglial cells, which are integral in the development of myelin, are particularly affected by alcohol exposure [62,63].

4.6. hCho and frontal lobe volume

The hippocampus voxel included the hippocampus and basal nuclear region (nucleus basilis of Meynert). During brain development, cholinergic neurons project from the nucleus basilis of Meynert to the frontal lobe [42]. Lauder and Schambra [64] reported that prenatal ethanol exposure in the mouse led to severely affected development of the forebrain CNS cholinergic system with deleterious effects on the synaptic targets of these cholinergic neurons, including reduced thickness of the cerebral cortex. The frontal lobe was significantly smaller (relative and absolute) in FAS/PFAS relative to all other groups (Fig. 7A). The hCho concentration in the voxel placed in the left hippocampus was near significantly lower in the FAS/PFAS (1.31±.23) group relative to all other groups combined (1.41±.21) (t=−1.7, P=.07) (Fig. 7B). hCho in the hippocampus/basal nuclear

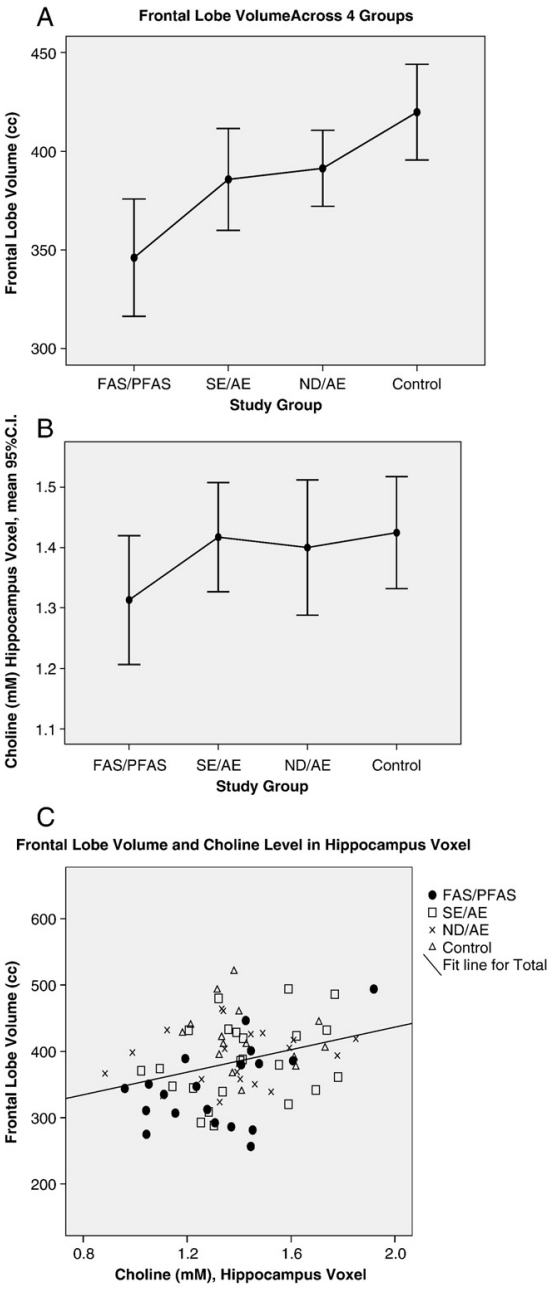

Fig. 7. Correlation between frontal lobe volume (cubic centimeter) and choline concentration (millimolar) in the hippocampus voxel containing the nucleus basilis of Meynert. The frontal lobe is innervated by cholinergic projections from the nucleus basilis of Meynert. (A) Frontal lobe volume was significantly smaller in FAS/PFAS relative to all other groups. (B) hCho in the hippocampus voxel was significantly lower in the FAS/PFAS group relative to all other groups. (C) Frontal lobe volume decreased significantly with decreasing hCho concentration in the hippocampus voxel.

voxel decreased significantly with decreasing size of the frontal lobe (Fig. 7C).

4.6.1. hCho and hippocampus size

The hippocampal system plays a critical role in learning and memory. The absolute size of the left hippocampus became significantly smaller as one advanced across the four study groups from the control group to the FAS/PFAS group (Fig. 8A). hCho in the voxel placed in the left hippocampus was near significantly lower in the FAS/PFAS (mean±S.D. 1.31±.23) group relative to all other groups combined (mean±S.D. 1.41±.21) (t=−1.7, P=.07) (Fig. 8B). hCho decreased significantly with decreasing absolute volume of the left hippocampus (Pearson correlation coefficient .22, P=.049) (Fig. 8C). The volume of the left hippocampus decreased significantly with increasing impairment on measures of visual memory using the Rey Complex Figure Test [65], verbal memory using the California Verbal Learning Test [66] and working memory on an N-back task [67]. Memory performance can be correlated with cholinergic activity in the hippocampus, measured by high affinity Cho uptake or choline acetyltransferase activity. Moreover, mechanical disruption of the septal projections to the hippocampus or lesions of the medial septal nuclei disturb memory retention [68]. Gibson et al. [69] reported that chronic prenatal ethanol exposure

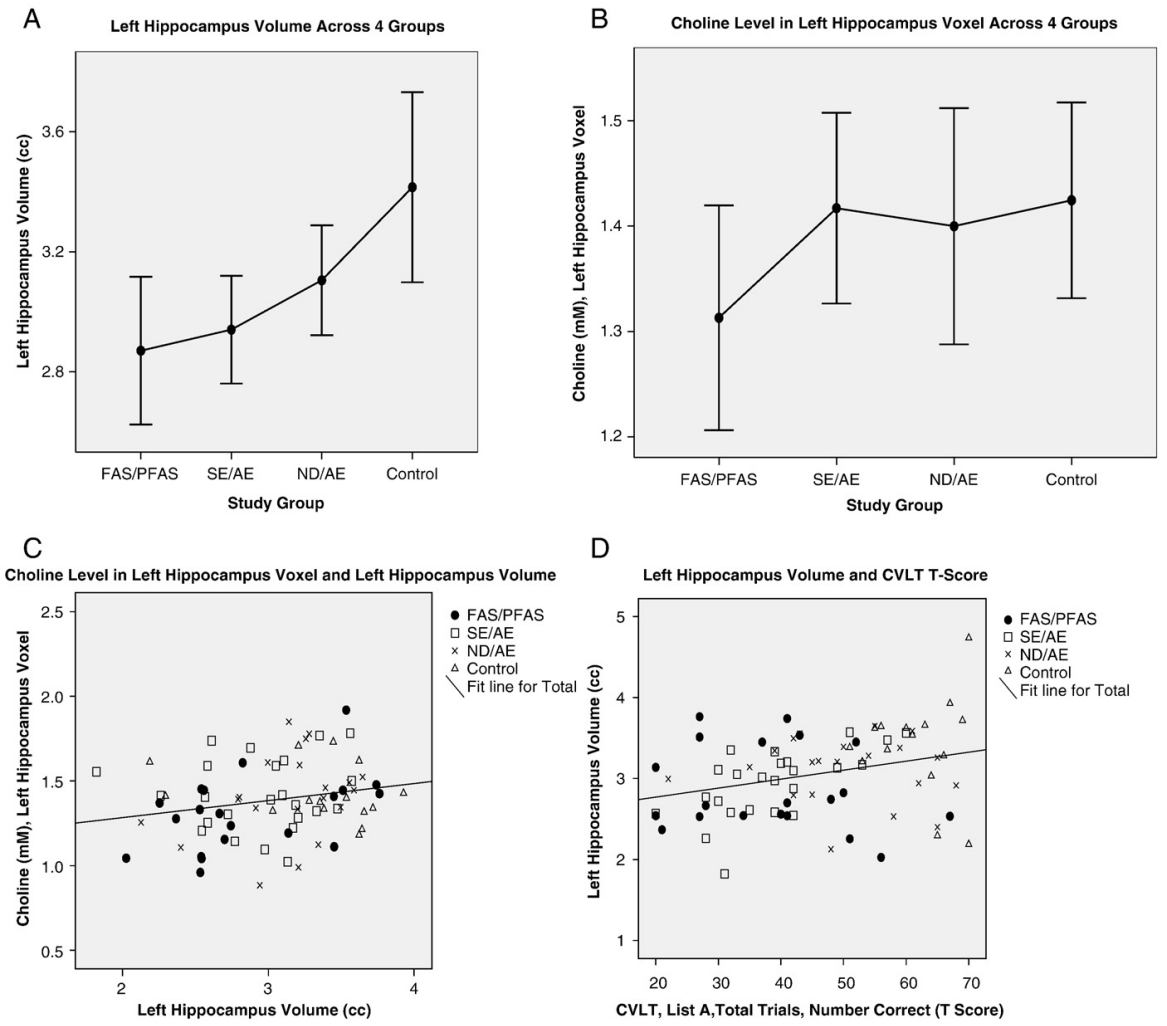

Fig. 8. Intercorrelations between hCho, hippocampus volume and cognition. (A) Hippocampus volume increased significantly as one advances across the four study groups from FAS/PFAS to controls. (B) hCho in the hippocampus voxel was lower in the FAS/PFAS group. (C) hCho decreased significantly with decreasing size of the hippocampus (Pearson correlation coefficient 0.22, P=.049.). (D) Performance on the California Verbal Learning Test decreased significantly with decreasing hippocampus volume (Pearson correlation coefficient 0.30, P=.007).

produced hyperactivity, decreased the brain and hippocampal weights with no change in body weight and decreased the number of hippocampal CA1 pyramidal cells by 25–30% in the guinea pig.

4.6.2. Morphogenetic roles of acetylcholine

Early work by Sulik and Johnston [70,71], Sulik [72], Schambra et al. [23] and Lauder and Schambra [64] illustrated the teratogenic impact of alcohol on the developing cholinergic system. As reported by Lauder and Schambra [64], in the adult nervous system, neurotransmitters mediate cellular communication within neuronal circuits. In developing tissues, neurotransmitters subserve growth regulatory and morphogenetic functions. Accumulated evidence suggests that ACho, released from growing axons, regulates growth, differentiation and plasticity of developing CNS neurons. In addition to intrinsic cholinergic neurons, the cerebral cortex and hippocampus receive extensive innervation from cholinergic neurons in the basal forebrain. Acute exposure to ethanol in early gestation (which prevents formation of basal forebrain cholinergic neurons) significantly compromises cortical development and produces persistent impairment of cognitive functions. The results of this study provide further evidence of the vulnerability of the cholinergic system in FASD and are particularly compelling considering recent promising intervention outcomes using neonatal and perinatal choline supplementation in FASD [73,74].

4.7. FASD MRS human literature

Very few MRS studies have been conducted to date in the field of FASD. Cortese et al. [22] conducted an MRI/MRS investigation of the caudate region in a very small population of children (seven FAS and two FAE by gestalt diagnosis, and four controls). The investigators reported that FAS and FAE were defined on prenatal alcohol exposure and facial dysmorphia, but did not report what facial dysmorphia distinguished their FAS and FAE groups. When the seven children with FAS were compared to the four controls, the FAS group (1) did not have significantly smaller total brain volumes; (2) did have significantly smaller absolute, but not relative caudate volumes; and (3) had significantly higher NAA/Cre and NAA levels in the caudate. No significant Cho or Cho/Cre differences were reported. The investigators used one-tailed *P* values for all tests of significance. In contrast to the FASD literature [75,76], FAS groups typically have significantly smaller brain volumes, by clinical definition. And in contrast to the general MRS literature [43], including the current FASD MRS study and the FASD MRS study conducted by Fagerlund et al. [21], neuronal dysfunction is typically associated with a decrease in absolute concentration of NAA, not an increase. Although Cortese et al. [22] reported comparisons between the two children with FAE and four controls, these samples were too small to provide clinically or statistically meaningful results.

Fagerlund et al. [21] conducted an MRS study on 10 adolescents/adults with FASD (three FAS, three PFAS and four ARND, using the Hoyme FASD diagnostic guidelines [77]) and 10 healthy controls. All subjects with FAS and PFAS had microcephaly. The controls were matched to the FASD group on head circumference. The FASD group had lower NAA/Cre and NAA/Cho ratios than the control group in several brain regions, but not in the regions that were the focus of this report (hippocampus and caudate). The authors noted, however, that the decreased NAA/Cre and NAA/Cho metabolite ratios appeared to be driven by higher Cho or Cre in the denominators, not by lower NAA in the numerators. Although their absolute metabolite intensities were subject to error, they noted that, on average, NAA was 7% higher and Cre and Cho were 14% higher in their FASD group relative to their control group. Separating numerator from denominator effects is problematic in studies reporting metabolite ratios. Prior to advancements in technology that now allow absolute metabolite levels to be computed, early studies, including the nonhuman primate study [16], had to assess Cho and NAA relative to Cre. The Cre was used as an internal standard with the hope that Cre reflected a stable metabolite across regions and individuals. But numerous studies [14,41,44,52,78] have since demonstrated that Cre varies by region and clinical status. The mean Cre concentration in the current study varied by as much as 9% between regions and study groups. The variability of these Cre concentrations had a marked impact on some of the metabolite ratios observed in the current study. For example, the mean absolute concentrations of wNAA and wCre were both 9% lower in the FAS/PFAS group than in the controls. But when these metabolites were presented as a ratio (wNAA/Cre), the mean wNAA/Cre level for the two groups was identical. Fagerlund et al. [21] did not observe significantly lower Cho/Cre in their FASD group relative to their control group. The current study would not have observed significantly lower wCho either if the three FASD groups (FAS/PFAS, SE/AE and ND/AE) had been combined and the Cho had been assessed as a ratio with Cre. The significantly low absolute concentration of wCho was unique to the FAS/PFAS group in the current study. Many factors differ between the two studies which likely contributed to the different outcomes. The Fagerlund et al. [21] study had a smaller sample size, used different FASD diagnostic criteria, matched their FASD and controls on a key diagnostic feature of FAS (microcephaly), combined their FASD groups and assessed metabolite ratios rather than absolute concentrations of the metabolites.

4.8. Limitations

A limitation of the current study is the use of a fixed-size voxel in brains that vary in size. A fixed-size voxel will include more surrounding tissue in a smaller brain than a larger brain. This, in turn, could influence the mean

metabolite concentration within the voxel, since metabolite concentrations vary normally by region and tissue type. wCho levels did not vary significantly with total brain size. hCho levels were positively correlated with total brain size. While secondary analyses suggest the lower mean hCho among the FAS/PFAS group was unlikely to be due entirely to partial voluming, the impact of partial voluming needs to be addressed in future studies. One might consider matching controls to cases on total brain size to eliminate the partial voluming problem, but in so doing, the definition of a healthy, typically developing comparison group is compromised if the subjects in the comparison group have microcephaly.

4.9. Conclusion

This study demonstrated that the FAS/PFAS group has significantly low Cho levels that may reflect white matter deficits in this group. NAA and Cre were comparable between the FASD groups and the controls. This study provides further evidence of the vulnerability of the cholinergic system in FASD and is particularly compelling what with the growing FASD literature on positive outcomes associated with choline supplementation.

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Functional magnetic resonance imaging outcomes from a comprehensive magnetic resonance study of children with fetal alcohol spectrum disorders

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Abstract A comprehensive neuropsychological/psychiatric, MR imaging, (MRI), MR spectroscopy (MRS), and functional MRI (fMRI) assessment was administered to children with fetal alcohol spectrum disorders (FASD) to determine if global and/or focal abnormalities could be identified, and distinguish diagnostic subclassifications across the spectrum. The four study groups included: 1. FAS/Partial FAS; 2. Static Encephalopathy/Alcohol Exposed (SE/AE); 3. Neurobehavioral Disorder/Alcohol Exposed (ND/AE); and 4. healthy peers with no prenatal alcohol exposure. fMRI outcomes are reported here. The neuropsychological/psychiatric, MRI, and MRS outcomes are reported separately. fMRI was used to assess activation in seven brain regions during performance of *N*-back working memory tasks. Children across the full spectrum of FASD exhibited significant working memory deficits and altered activation patterns in brain regions that are known to be involved in working memory. These results demonstrate the potential research and diagnostic value of this non-invasive MR tool in the field of FASD.

Keywords Fetal alcohol spectrum disorder (FASD) · Functional magnetic resonance imaging (fMRI) · Working memory · FASD 4-Digit Diagnostic Code · *N*-back

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Introduction

Fetal alcohol syndrome (FAS) is a permanent birth defect syndrome caused by maternal alcohol consumption during pregnancy. FAS is defined by growth deficiency, a unique cluster of minor facial anomalies, and central nervous system (CNS) dysfunction and/or structural brain abnormalities [1]. The cognitive/behavioral problems in this condition stem from prenatal brain damage. Not all individuals with prenatal alcohol exposure present with measurable CNS dysfunction or structural brain abnormalities,

and not all who present with measurable CNS dysfunction or structural brain abnormalities have FAS. Recently, the term Fetal Alcohol Spectrum Disorders (FASD) was coined to depict the spectrum of outcomes observed among individuals with prenatal alcohol exposure. FASD is not a medical diagnosis. Rather, diagnoses like FAS, Partial FAS, Static Encephalopathy/Alcohol Exposed, and Neurobehavioral Disorder/Alcohol Exposed fall under the umbrella of FASD. The degree of brain damage among individuals with prenatal alcohol exposure may vary from microcellular and neurochemical aberrations to gross structural anomalies. Similarly, cognitive/behavioral dysfunction varies along the full continuum from mild developmental delay or learning disabilities to global developmental disability. The specificity of the FAS facial phenotype to prenatal alcohol exposure lends credence to the clinical judgment that the cognitive and behavioral dysfunction observed in individuals with FAS is due, at least in part, to brain damage caused by a teratogen [2–4]. Unfortunately, without the unique facial phenotype of FAS or at least a severe or clinically obvious expression of brain damage, the neurodevelopmental disabilities of an individual affected by prenatal alcohol exposure often go unrecognized and inappropriately served [5].

Many individuals with prenatal alcohol exposure exhibit cognitive difficulties and significant maladaptation that prevent them from leading productive, independent lives [6, 7]. Across the population, the profile of cognitive dysfunction among individuals with prenatal alcohol exposure is highly variable, though there are some commonalities in functional compromise among subgroups, and conceptual models of overarching deficits have been proposed [8]. However, no single behavioral phenotype specific to alcohol teratogenicity has been described. Without a behavioral phenotype specific to the teratogen alcohol, attributing an alcohol-exposed child's dysfunction to brain damage is often questionable at a clinical level [4]. If indisputable evidence of brain damage (e.g., alterations in neurostructure, neurometabolites and/or neuroactivation) could be found in these individuals, and linked to behavioral deficit, diagnostic efforts could be improved. The "disability" of these alcohol-exposed children would be clearly established, and help facilitate eligibility for needed services. Further, if specific alterations in neurostructure, neurometabolites, and/or neuroactivation could be linked to clinically meaningful, discrete neuropsychological deficits, development of appropriate intervention programs could be accelerated.

The overall goal of this research study was to determine if magnetic resonance imaging, (MRI), magnetic resonance spectroscopy (MRS), and/or functional MRI (fMRI) could serve as non-invasive methods for definitively identifying global and/or focal brain abnormality across the full continuum of FASD, and distinguish diagnostic subclassifications within the spectrum. The results of this comprehensive study are presented in four separate reports: fMRI (presented here), and the neuropsychological/behavioral [9], MRI (submitted for publication), and MRS [10] outcomes reported separately.

fMRI is a potentially powerful tool that can assess regional brain activation in response to performance on specific cognitive, perceptual, or motor tasks. Many studies, spanning a broad array of disease states and disorders, have used this tool to document activation that is different in intensity and/or spatial extent in subjects with brain damage and/or impairment on the specific tasks being assessed [11–13]. Only three FASD fMRI studies have been published to date. Significant differences in brain activation patterns were observed between FASD and Control groups during verbal learning [14], response inhibition [15], and spacial working memory [16] tasks. All of these tasks require higher-order cognitive abilities that are often deficient in individuals with FASD [17–21]. All three studies clearly demonstrated the value of fMRI in this clinical population. The present study extends this line of inquiry to nonspatial working memory, using an fMRI *N*-back paradigm. Working memory is the ability to hold and manipulate information online in the brain [22, 23]. The constituent processes involved in working memory are encoding, rehearsal, storage, and executive processes on the contents of stored memory [13]. Working memory is subserved by a neurocognitive network comprising regions involved in attention (anterior cingulate), executive function (dorsolateral prefrontal cortex), and short-term mnemonic strategies (parietal cortex and precuneous) [24–26].

Materials and methods

Subjects and study groups

The protocol was approved by the University of Washington Human Subjects Review Board. The three FASD groups were selected from among 1,200 patients previously diagnosed by an interdisciplinary team in the WA State FAS Diagnostic & Prevention Network (FAS DPN) of clinics using the FASD 4-Digit Code [27, 28]. Briefly, the four digits of the FASD 4-Digit Code reflect the magnitude of expression of the four key diagnostic features of FASD, in the following order: (1) growth deficiency, (2) characteristic FAS facial phenotype, (3) CNS structural/functional abnormalities, and (4) prenatal alcohol exposure (Fig. 1). The magnitude of expression of each feature is ranked independently on a four-point Likert scale, with 1 reflecting complete absence of the FASD feature and 4 reflecting a strong "classic" presence of the FASD feature. Each Likert

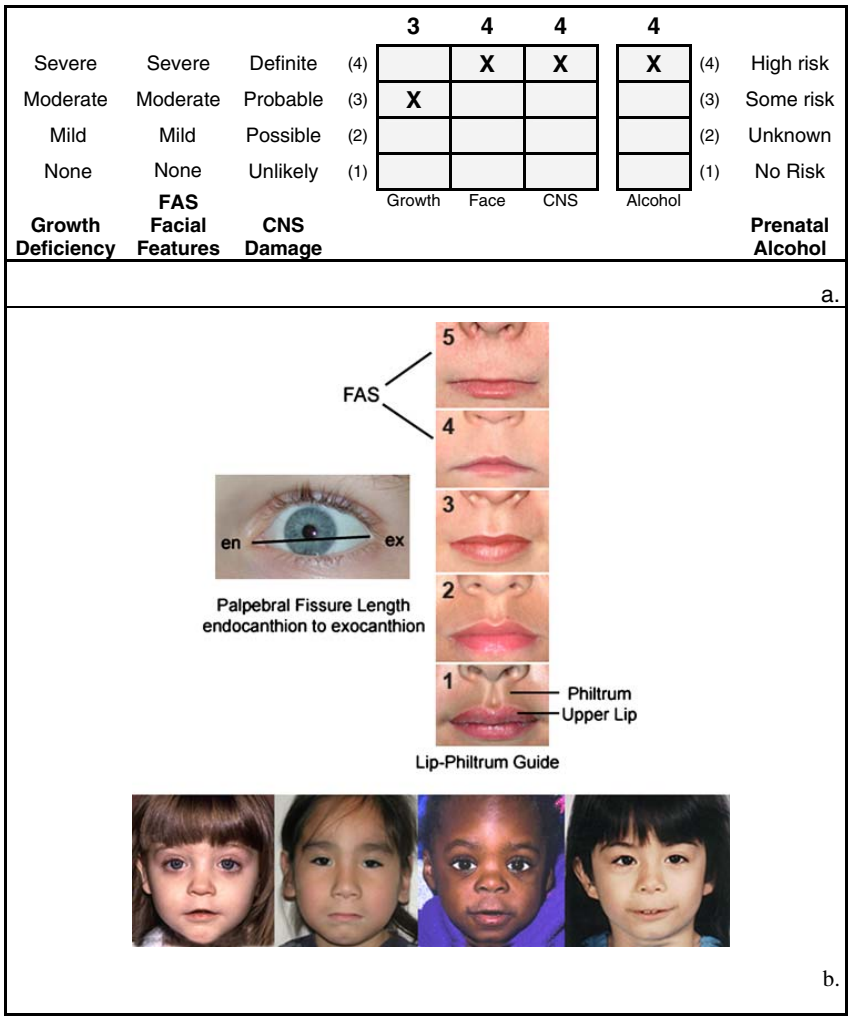

Fig. 1 **a** FASD 4-Digit Diagnostic Code grid. FASD is defined by growth deficiency, specific FAS facial features, evidence of CNS damage and prenatal alcohol exposure. The 4-Digit Code ranks each of these areas on four-point, case-defined, Likert scales. The 4-Digit Code (*3444*) inserted in the grid is one of 12 codes that meet the diagnostic criteria for FAS. **b** FASD 4-Digit Code FAS facial phenotype. The rank 4 FAS facial phenotype as defined by the 4-Digit Diagnostic Code requires the presence of all three of the following anomalies: (1) palpebral fissure lengths 2 or more standard deviations below the norm mean; (2) a smooth philtrum (rank 4 or 5 on the Lip–Philtrum Guide), and (3) a thin upper lip (rank 4 or 5 on the Lip–Philtrum Guide). Examples of the rank 4 FAS facial phenotype for Caucasian, Native American, African American, and Asian American children are shown. © 2009 University of Washington. Reproduced with permission from Susan Astley, Ph.D.

rank is specifically case defined. There are 256 possible 4-Digit Diagnostic Codes, ranging from 1,111 to 4,444. Each 4-Digit Diagnostic Code falls into one of 22 unique clinical diagnostic categories (labeled A through V). Seven of the 22 diagnostic categories (4-Digit Categories A–C and E–H) fall under the umbrella of FASD (A. FAS/Alcohol Exposed, B. FAS/Alcohol Exposure Unknown, C. Partial FAS/Alcohol Exposed, E–F. Static Encephalopathy/Alcohol Exposed, and G–H. Neurobehavioral Disorder/Alcohol Exposed). The three FASD study groups in the current study represent these FASD diagnostic categories. The control population was selected primarily from a large cohort of children enrolled at birth in a University of Washington study of typical development conducted through the Department of Speech and Hearing Sciences. With the enrollment of each child in the FAS/PFAS group, a child matched on age (within 6 months), gender, and race was randomly identified and invited to enroll from the eligible SE/AE, ND/AE and Control populations. A stratified–randomized block design was used to select children with FAS/PFAS from the eligible clinic population to achieve an equal distribution of gender, the full eligible age range (8–15.9 years), and a racial distribution that matched the clinic population.

The study enrollment procedure produced a sample of 81 children in the overall MR study [9]. A representative subset of 71 children contributed data to the fMRI component of this study (Table 1). Each of the four fMRI study groups had 13–22 subjects successfully balanced on age, gender, and race. Each study group spanned the full

Table 1 Sociodemographic and FASD 4-Digit Diagnostic Code profile of the four study groups that participated in the fMRI study

Characteristic		1. FAS/PFAS[f] *N*=16	2. SE/AE *N*=22	3. ND/AE *N*=20	4. Control *N*=13
Gender: *n* (%)[a]	Female	7 (43.8)	8 (36.4)	10 (50.0)	6 (46.2)
Age at enrollment (years): mean (SD)[b]		13.3 (2.0)	12.4 (2.0)	12.5 (2.2)	12.9 (2.6)
Race: *n* (%)[c]	Caucasian	11 (68.8)	10 (45.5)	12 (60.0)	10 (60.6)
	Black	4 (25.0)	3 (13.6)	5 (25.0)	2 (15.4)
	Other	1 (6.3)	9 (40.9)	3 (15.0)	1 (7.7)
Growth rank from 4-Digit Code: *n* (%)	1. none	9 (56.3)	13 (59.1)	12 (60.0)	12 (92.3)
	2. mild	1 (6.3)	2 (9.1)	6 (30.0)	1 (7.7)
	3. moderate	4 (25.0)	3 (13.6)	1 (5.0)	0 (0.0)
	4. severe	2 (12.5)	4 (18.2)	1 (5.0)	0 (0.0)
Face rank from 4-Digit Code: *n* (%)	1. none	0 (0.0)	3 (13.6)	6 (30.0)	9 (69.2)
	2. mild	0 (0.0)	19 (86.4)	14 (70.0)	4 (30.8)
	3. moderate	3 (18.8)	0 (0.0)	0 (0.0)	0 (0.0)
	4. severe[d]	13 (81.3)	0 (0.0)	0 (0.0)	0 (0.0)
CNS ranks 1–3 from 4-Digit Code					
Level of functional impairment: *n* (%)	1. none	0 (0.0)	0 (0.0)	0 (0.0)	13 (100.0)
	2. moderate	0 (0.0)	3 (13.6)[g]	20 (100.0)	0 (0.0)
	3. severe	16 (100.0)	19 (86.4)	0 (0.0)	0 (0.0)
CNS rank 4 from 4-Digit Code	Structural/neurological abnormality present: *n* (%)	9 (56.3)	6 (27.3)	0 (0.0)	0 (0.0)
Alcohol rank from 4-Digit Code: n (%)	1. No exposure	0 (0.0)	0 (0.0)	0 (0.0)	13 (100.0)
	2. Unknown exposure[e]	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
	3. Confirmed exposure. Level moderate or unknown	5 (31.3)	11 (50.0)	11 (55.0)	0 (0.0)
	4. Confirmed exposure: Level high	10 (62.5)	11 (50.0)	9 (45.0)	0 (0.0)

A comprehensive profile of the entire study sample is presented in Astley et al. [9]

[a] Percent female: chi-square=0.8 (*df* 3), p=0.84

[b] Mean age: ANOVA $F(3, 67)$ 3.2, p=0.56

[c] Percent Caucasian: chi-square=4.0 (*df* 3), p=0.26

[d] Definition of rank 4 FAS face: palpebral fissure lengths 2 or more SDs below the mean norm, and lip and philtrum are Rank 4 or 5 on the Lip–Philtrum Guide [27]

[e] The one child with unknown prenatal alcohol exposure had full FAS

[f] Four of the 16 subjects in group 1 had full FAS using the FASD 4-Digit Code. Nine of the 12 PFAS had rank 4 faces, but received a diagnosis of PFAS because of their absence of growth deficiency (growth rank 1)

[g] All three children with moderate functional impairment had structural evidence of brain abnormality (microcephaly)

age range of 8.0 to 15.9 years at the time of enrollment. The diagnostic features specific to each group were as follows:

1. Children in Group 1 had a 4-Digit diagnosis of FAS or Partial FAS (*FAS/PFAS*) (e.g., 4-Digit Diagnostic Categories A, B, C: with Growth Ranks 1–4, Face Ranks 3–4, CNS Ranks 3 and/or 4, and Alcohol Ranks 2–4) (Fig. 1). Alcohol Rank 2 (unknown exposure) could only be present if the child had a diagnosis of full FAS because the Rank 4 FAS facial features are so specific to prenatal alcohol exposure [3, 29]. Since the only clinical difference between FAS and PFAS in this study was the presence of growth deficiency in the former, FAS and PFAS were combined. Children in Group 1 had severe cognitive/behavioral dysfunction and the FAS facial phenotype.
2. Children in Group 2 had a 4-Digit diagnosis of Static Encephalopathy/Alcohol Exposed (*SE/AE*) (e.g., 4-Digit Diagnostic Categories E and F: with Growth Ranks 1–4, Face Ranks 1–2, CNS Ranks 3 and/or 4, and Alcohol Ranks 3–4). Children in Group 2 had severe cognitive/behavioral dysfunction, comparable to Group 1, but did not have the FAS facial phenotype.
3. Children in Group 3 had a 4-Digit diagnosis of Neurobehavioral Disorder/Alcohol Exposed (*ND/AE*) (e.g. 4-Digit Diagnostic Categories G and H: with Growth Ranks 1–4, Face Ranks 1–2, CNS Rank 2, and Alcohol Ranks 3–4). Children in Group 3 had prenatal alcohol exposure comparable to Groups 1 and 2, but had only mild to moderate cognitive/behavioral dysfunction, and did not have the FAS facial phenotype.

4. Children in Group 4 (Healthy *Controls*/No Alcohol Exposure) were selected based on parental report that the child was healthy, had no academic concerns, and no prenatal alcohol exposure (e.g., 4-Digit Diagnostic Category V: with Growth Ranks 1–2, FAS Face Ranks (no restrictions), CNS Rank 1, Alcohol Rank 1).

Using the FASD terminology introduced by the Stratton et al. [6], the SE/AE group most closely reflects 'severe ARND' and the ND/AE group reflects 'mild ARND'. A comprehensive analysis of the between-group differences of these diagnostic features is presented in the neuropsychological/behavioral report for this study [9].

Study participation

Participation in the study involved five visits over a 4 to 6 week study period. The neuropsycological and sociodemographic data were collected during visits 1 and 2. The MR data were collected during visits 3 and 4. Outcomes of the neuropsycological assessments were shared with the caregivers on visit 5, and submitted to the child's medical record with caregiver consent.

Sociodemographic and clinical assessment

A comprehensive sociodemographic and health/medication history of each child was obtained by parent interview and record review. Information included birth data, growth, and all prenatal and lifetime exposures and adverse events. For subjects with FASD, most information was obtained at the time of their FASD diagnostic evaluation. All controls had a reported absence of prenatal alcohol exposure. All children had a standardized digital facial photograph taken at the time of enrollment. The facial photographs were analyzed using the FAS Facial Analysis Software [30] to document the magnitude of expression of the FAS facial phenotype [29]. A more detailed methodology and analysis of the sociodemographic and FASD diagnostic outcomes, including prenatal alcohol exposure histories, are presented in the neuropsychological/behavioral report from this study [9].

Neuropsychological and psychiatric assessments

A detailed description of the assessment battery and a comprehensive analysis of the between-group differences in neuropsychological outcome are presented in the neuropsychological/behavioral report for this study [9]. Briefly, a comprehensive, standardized assessment battery was administered to each child/caregiver by a psychologist masked to group assignment. The assessment battery was designed to capture the domains of potential neuropsychological impairment seen as the result of the typically diffuse brain damage arising from alcohol teratogenesis [8, 20, 31–34]. The neuropsychological/behavioral outcomes served to profile the study groups and confirm the groups were clinically and statistically distinct from one another; fundamental to the interpretation of the MR outcomes.

MR scanner

All scans (MRI, MRS, and fMRI) were acquired using a General Electric 1.5 Tesla scanner in the Diagnostic Imaging Sciences Center (DISC) at the University of Washington.

MRI and MRS

The MRI and MRS [10] components of this study are reported separately. Briefly, MRI was used to measure the size of the following brain regions: total brain, frontal lobe, caudate, putamen, hippocampus, corpus callosum, and cerebellar vermis. MRS was used to measure the concentrations of three neurometabolites: (1) choline, a marker of cell membrane stability and myelination, (2) N-acetyl aspartate, a neuronal or axonal marker, and (3) creatine, a marker of metabolic activity in selected brain regions.

fMRI: *N*-back working memory task

An existing fMRI paradigm [35] was modified for this clinical population to assess activation in specific brain regions during working memory. In agreement with other fMRI studies of working memory [24–26], testing with normal controls using this paradigm demonstrated consistent activation of the dorsolateral prefrontal cortex (DLPFC). The *N*-back task [36] involved viewing a series of images (e.g., faces), one at a time, and deciding whether the present image matched the image presented *n* images back, where *n* is 1 or 2. The images were four male and four female faces. *N*-back paradigms often use numbers for stimuli. Because research indicates alcohol-affected children often have math deficits and difficulty with numbers, faces were selected as the stimuli. Two tasks were developed, one using a 0-back and 1-back condition, and one using a 0-back and 2-back condition. The 0-back (control) condition required the subject to press the button whenever a man's face was presented. The 1-back (activation) condition required the subject to press the button whenever the face they were currently viewing was the same as the one immediately preceding it. The 2-back (activation) condition required the subject to press the button whenever the face they were currently viewing was the same as the one presented two images back. The subjects were presented with a series of

80 images (one at a time) for each of the 1-back and 2-back tasks. The 80 images for the 1-back task were presented in the following order: the first 20 images represented the 0-back condition with seven man's faces presented in random order. The next 20 images represented the 1-back condition with six randomly placed images meeting the 1-back criteria. The next 20 images returned to the 0-back condition with seven man's faces presented in random order. The final 20 images presented the 1-back condition with six randomly placed images meeting the 1-back criteria. The 2-back task followed the same pattern alternating the 0-back and 2-back conditions. Of the 80 images, 26 were positive (the subject should press the button because the image met the *N*-back condition) and 54 were negative (the subject should not press the button because the image did not meet the *N*-back condition). The *N*-back tasks were scored based on the number of true-positive, true-negative, false-positive, and false-negative responses recorded across the 80 images. Subject's reaction times (ms) also were measured.

To collect meaningful activation data during an *N*-back task, it is essential for subjects to be actively engaged in the task while lying perfectly still in the scanner. To prepare the child for the fMRI session in the scanner, the child was acclimated to the scanner environment in the mock scanner. A single practice session of the *N*-back task was administered to the child while in the mock scanner, to confirm the child understood the task well enough to perform it in the real scanner. Children performing with >65% accuracy on the practice version of the 1-back task were scanned using the 1-back condition. Children performing with >65% on the practice version of the 2-back task were scanned using the 2-back condition. Children performing at <65% accuracy on the *N*-back tasks were unlikely to perform the tasks in the scanner so as to yield meaningful activation data. Once in the scanner, only data from *N*-back tasks where the number of true-positive and true-negative responses were >65% correct were used to assess activation.

fMRI acquisition and analysis

Scans were acquired on a 1.5 T GE Signa MR scanner, using a 21 slice blood oxygenation level-dependent (BOLD) EPI pulse sequence with the following parameters: gradient echo pulse, TR=3,000 ms, TE=50 ms, flip angle=90, matrix=64 X 64, FOV=24, slice thickness=6.0 mm, 0 gap. Two scans were acquired; one during the 1-back task and one during the 2-back task. Each scan lasted 5 min and 18 s. The 1-back task included two repetitions of the following: 18 s of fixation, followed by 6 s of instruction, 60 s of 0-back (control) condition, 6 s of instruction, and 60 s of 1-back (activation) condition. The scan ended with another 18 s of fixation. The 2-back task followed the same pattern, using the 2-back condition for the activation condition.

Data from the fMRI scans were transferred from the scanner to the UNIX workstation, globally normalized, and archived on CD-ROMs. fMRI scans were analyzed using the software package MEDx 3.2, a multimodal radiological image processing program (Sensor Systems, Sterling, VA), run on a workstation with Linux operating system software. Motion detection was performed using a center-of-intensity plot. Scans with greater than five volumes with motion that exceed 0.3 mm from the center of intensity in any plane were considered unusable.

For scans with motion not exceeding this threshold, motion correction was performed, using the AIR algorithm [37, 38] (version 3.08, including the alignlinear and alignwarp programs). This algorithm minimizes the variance of the ratio of the intensities of two images. A gradient descent search was performed to arrive at a global minimum. All images were registered to the same reference image normalized to Tailarach space. A linear rigid body (six parameter) model, with trilinear interpolation was used. Pixel-by-pixel linear detrending was applied to correct for gradual drift in pixel intensity during the time course of the series. Paradigms were then applied, assigning individual volumes to either the control (0-back) or activation (1- or 2-back) conditions. Based on examination of the hemodynamic lag, 3 s of data were omitted from the beginning of the series. A statistic summarizing the activation difference between control and activation conditions was computed for each voxel. The statistic was computed as that of a two-sample *t*-test, and was subsequently transformed to a *Z*-score via the Fisher transformation [11]. Active voxels were then identified as those with *Z*-scores exceeding a fixed threshold (a *z*-score>3). Previous experience with normal subjects indicated that threshold values in the range of 2.4–6.0 (corresponding to 1-tailed *P*-value of <0.0082) provide informative, reliable binary activation maps.

Group maps were first produced for each of the four study groups, and areas of primary activation (for any group) were identified. Consistent with previous literature, these regions included left and right anterior cingulate, parietal lobe, particularly the anterior parietal region, dorsolateral prefrontal, inferior frontal, middle frontal and precentral regions of the frontal lobe (Fig. 2). Using the ROIs identified on the template brain, two measures of activation were computed for each subject for each of these brain regions: (1) the number of voxels whose *z* value exceeded the threshold (*z*=3.0; cluster corrected), and (2) the average z score within the region. For each subject and each region, number of activated voxels (i.e., those whose z value exceeded the threshold) was divided by the number of voxels in the region, yielding a measure reflecting the percent of activated voxels within the region. Comparison

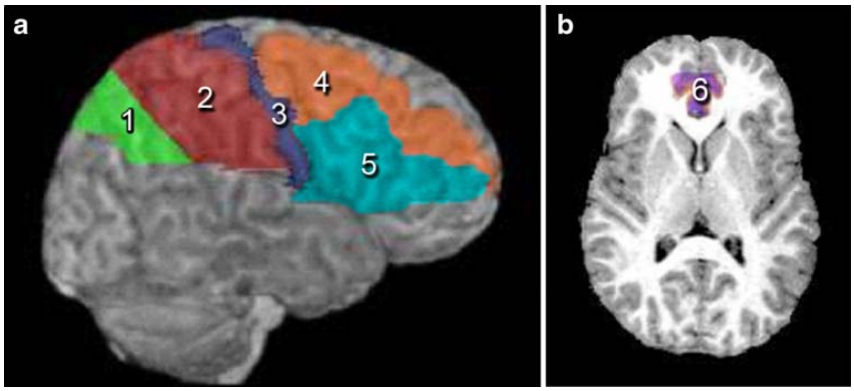

Fig. 2 Regions of interest: *1* posterior parietal lobe, *2* anterior parietal lobe, *3* precentral gyrus, *4* middle frontal gyrus, *5* inferior frontal gyrus, and *6* anterior cingulate gyrus

of groups was performed using traditional statistical techniques on these measures.

For clarity, the following nomenclature will be used throughout the remainder of this report. The term 'activation' refers to the difference in activation between the control condition (0-back) and the activation condition (1- or 2-back). The term 'task' (as in 1-back task) refers to the 0-back and 1-back conditions that together make up the 1-back task. The term 'condition' (as in 1-back condition) refers to the 1-back condition within the 1-back task.

fMRI hypotheses

In this report, the neural substrates of working memory in children with FASD were investigated. Given that subjects with FASD have significant deficits in working memory [16] and executive function [17–21] it was hypothesized they would show significant deficits in performance on the *N*-back tasks. It was also hypothesized that they would show significant alterations in activation in brain regions known to be involved in working memory, since prior FASD fMRI studies have shown activation alterations during memory and response inhibition tasks [14–16]. Trends across the four study groups were hypothesized because the neuropsychological/psychiatric report for this study [9] confirmed the four study groups were clinically distinct and increasingly more affected as one advanced across the four groups from the Controls to the FAS/PFAS.

1. Performance on the 1-back and 2-back conditions of the *N*-back tasks will decline as one advances across the four study groups from Controls to ND/AE to SE/AE to FAS/PFAS. Measures of performance include number of true-positive, true-negative, false-positive, and false-negative responses, and subjects' reaction times (seconds) for positive responses.
2. Activation (across the selected brain regions; primarily the DLPFC) will increase or decrease as one advances across the four study groups from Controls to ND/AE to SE/AE to FAS/PFAS. Two measures of activation (summarizing the difference in activation between control and activation conditions) were assessed: (1) the mean activation *z*-score across all voxels in a brain region, and (2) the percent of voxels with an activation *z*-score >3 in a brain region.

It was not specified, a priori, whether activation levels among the FASD groups would be higher or lower than the Control group, because this is the first FASD fMRI study of visual working memory, and impairment in brain function can manifest as higher or lower activation relative to a healthy Control group.

Statistical analyses

Chi-square and oneway ANOVA were used to confirm race, gender and mean age were effectively balanced across the four study groups. ANOVA, including multivariate and repeated measures, were used to test hypotheses 1 and 2. Full factorial designs, which included all main effects and all interactions for within-subjects factors were used. Factors included group (FAS/PFAS, SE/AE, ND/AE, Control), Task (1-back, 2-back), Condition (control, activation), Region (middle frontal gyrus, DLPFC, posterior parietal lobe, anterior parietal lobe, inferior frontal gyrus, precentral gyrus, anterior cingulate gyrus), and hemisphere (right, left). A priori contrasts were used to test for differences among the levels of a factor. For example, a polynomial contrast was included in the ANOVA to determine if mean outcomes changed incrementally as one advanced across the four study groups from Control to FAS/PFAS. Significant linear trends across these four study groups were observed in the magnitude of neuropsychological impairment [9] and reduction in size of brain regions. If significant differences existed among group means, the Duncan post hoc range test was used to identify which groups differed. The Duncan test makes pairwise comparisons using a stepwise procedure. Means are ordered

from highest to lowest, and extreme differences are tested first. The Duncan test sets a protection level for the error rate for the collection of tests and identifies homogeneous subsets of means that are not different from one another at the $p=0.05$ level. Two-tailed p-values of 0.05 were used throughout the analyses.

Results

Proportion of subjects who were able to participate successfully in *N*-back-fMRI tasks

Seventy-one of the 81 children enrolled in the larger MR study were able to participate successfully in the *N*-back tasks and fMRI evaluation (Table 2). To obtain valid activation data, the subject had to: (1) provide adequate performance/effort during the *N*-back tasks (the child had to be engaged throughout the task, even if they failed to get the correct answers), and (2) lay sufficiently still throughout the scan. Because of the cognitive/behavioral impairment of our FASD study groups, there was concern that many would not be able to successfully participate in the fMRI portion of the study. Only one subject in each study group failed to demonstrate adequate performance/effort during the 1-back task (Table 2). Adequate performance/effort was defined as >65% correct true-positive and true-negative responses with active response throughout the task. One to four subjects per group failed to demonstrate adequate performance/effort during the more difficult 2-back task. Subjects in the alcohol-exposed groups were more likely to perform below criteria on the 2-back task than Controls, but the group contrasts were not significantly different. The subjects in the FAS/PFAS were more likely to have difficulty in adapting adequately to the scanner (entering the scanner or lying still within the scanner) in order to produce valid fMRI data, than the remaining groups, but this contrast was also not statistically significant (Table 2). Overall, the subset of 71 children (16/20 FAS/PFAS, 22/24 SE/AE, 20/21 ND/AE and 13/16 Controls) who were able to participate successfully in this fMRI study were highly representative (clinically and sociodemographically) of the full set of 81 children enrolled in the larger MR study.

As described in the neuropsycological/behavioral report from this study [9], two subjects in the FAS/PFAS group had agenesis (ACC) and hypogenesis (HCC) of the corpus callosum. These anomalies were known prior to enrollment into the study. The subject with ACC was able to provide adequate performance on both *N*-back tasks, but valid activation data could not be obtained. The subject with HCC was not able to provide adequate performance on either *N*-back task, thus activation data were not assessed. As a consequence, data on these two individuals are not included in this report.

N-back performance across the four study groups (hypothesis 1)

N-back performance did not vary by age, race, or gender in this study population. *1-back Task.* Performance and reaction times for the control condition (0-back) were comparable between the four groups (Table 3). The FAS/PFAS group had significantly poorer performance and longer reaction times than the Control group on the 1-back condition. Performance on the 1-back condition decreased and reaction times increased linearly as one advanced across the four groups from Control to FAS/PFAS. *2-back Task.* Performance and reaction times for the control condition (0-back) were again comparable between the four groups (Table 4). The FAS/PFAS group had significantly

Table 2 Number of subjects able to participate successfully in the *N*-back tasks and the fMRI scan across the four study groups

fMRI—*N*-back task participation	1. FAS/PFAS *N*=20 *N* (%)	2. SE/AE *N*=24 *N* (%)	3. ND/AE *N*=21 *N* (%)	4. Control *N*=16 *N* (%)
1-back task				
Unable to enter or lie still in the scanner	4 (20.0)	1 (4.2)	0 (0.0)	2 (12.5)
Entered scanner				
But did not provide adequate performance/effort[a]	1 (5.0)	1 (4.2)	1 (4.7)	1 (6.3)
And provided adequate performance/effort[a]	15 (75.0)	22 (91.6)	20 (95.3)	13 (81.3)
2-back task				
Unable to enter or lie still in the scanner	5 (25.0)	2 (8.3)	2 (9.5)	2 (12.5)
Entered scanner				
But did not provide adequate performance/effort[a]	2 (10.0)	4 (16.7)	3 (14.3)	1 (6.3)
And provided adequate performance/effort[a]	13 (65.0)	18 (75.0)	16 (76.2)	13 (81.3)

[a] Adequate performance on *N*-back was defined as ≥65% correct true-positive and true-negative responses

poorer performance and longer reaction times than the Control group on the 2-back condition. Performance on the 2-back condition decreased and reaction times increased linearly as one advanced across the four groups from Control to FAS/PFAS. *1-back Condition versus 2-back Condition*. In general, children in the FASD study groups performed more poorly with longer reaction times during the more difficult 2-back condition relative to the 1-back condition (Table 5). The Control group performed comparably across 1-back and 2-back conditions, but had significantly longer reaction times during the more difficult 2-back condition.

Activation by brain region across the four study groups during *N*-back tasks (hypothesis 2)

Pattern of activation across brain regions Activation patterns did not vary by age, race or gender in this study population. The level of brain activation during the *N*-back conditions, relative to the control condition, increased across the brain regions in the following order: precentral gyrus, anterior cingulate gyrus, anterior parietal lobe, inferior frontal gyrus, posterior parietal lobe, DLPFC, and middle frontal gyrus (Figs. 3a, b, Tables 6 and 7). This regional pattern of activation was observed bilaterally for both the 1-back and 2-back tasks across each study group. In general, among the Controls, the mean level of activation was significantly greater bilaterally in the anterior parietal lobe, inferior frontal lobe, posterior parietal lobe, DLPFC, and middle frontal gyrus relative to the region with the lowest level of activation (precentral gyrus) (Table 7). Comparable results were obtained regardless of which activation outcome variable was used (mean percent of voxels with a *z*-score>3 in each brain region, or mean *z*-score across all voxels in a brain region) (Table 7). Activation patterns did not vary significantly by age, race, or gender in this study population.

1-back task Activation Across Groups. The level of activation (mean percent of voxels with *z*-scores>3) during the 1-back condition, relative to the control condition, was comparable across all study groups (Table 6, Fig. 3a). The level of activation (when measured as the mean activity *z*-score across all voxels within each brain region) during the 1-back task was also comparable across all study groups (data not shown). *Right versus Left Hemisphere Activation*. No significant contrasts were observed between mean activation levels in the right versus left hemispheres of each brain region within each group during the 1-back task. *Activation and 1-back Task Performance.* The level of activation in each region was not significantly correlated with any measure of performance on the 1-back task. All Pearson Correlation Coefficients had two-tailed *p*-values> 0.05 (data not presented).

2-back task Activation across Groups. Activation levels (mean percent of voxels in each brain region with activity *z*-scores>3) during the 2-back condition, relative to the control condition, were significantly lower in the FAS/PFAS group than the Control group in the right posterior parietal lobe, right DLPFC, and right middle frontal regions (Fig. 3b, Table 7). Activation levels (when measured as mean activity *z*-score across all voxels in each brain region) during the 2-back task were significantly lower in the FAS/PFAS group than the Control group in the right inferior frontal gyrus, right posterior parietal lobe, right DLPFC, and right middle frontal regions (Table 7). Activation levels increased significantly in these regions as one advanced across the four groups from FAS/PFAS to Control. *Right versus Left Hemisphere Activation*. When significant contrasts were observed between the FAS/PFAS and Control groups, it always involved structures on the right side of the brain. In general, activation was consistently higher (although not statistically significantly) in the right versus left sides of the posterior parietal lobe, DLPFC, and middle frontal gyrus among the Controls during the 2-back task (Table 7). A similar, but weaker pattern was observed among the ND/AE and SE/AE groups. The pattern reversed (left comparable to or higher than right) among the FAS/PFAS group. *Activation and 2-back Task Performance.* Performance on the 2-back task was significantly correlated with activation level in several brain regions. More specifically, the higher the activation (mean percent of voxels with *z*-scores>3) in the R. and L. DLPFC, and R. and L. middle frontal gyrus, the lower the number of error responses (false-positives and false-negatives combined) on the 2-back task. Statistically significant Pearson correlation coefficients ranged from −0.25 to −0.28.

1-back task versus 2-back task Among Controls, activation (mean % of voxels with *z*-scores>3) was significantly higher (2 to five-fold higher) in the 2-back task (2-back condition relative to control condition) than in the 1-back task (1-back condition relative to the control condition). This was observed in all areas except the anterior cingulate and precentral regions (Table 8, Figs. 3a–c). Among the FAS/PFAS subjects, activation (mean % of voxels with *z*-scores>3) was not significantly higher (less than two-fold higher) in 2-back task relative to 1-back task across all brain regions (Table 8, Figs. 3a–c). As one advanced across the four study groups, the number of brain regions that showed a significant increase in activation in 2-back task relative to 1-back task increased (Table 8). The most marked contrasts in activation between 1-back and 2-back tasks occurred in the middle frontal, DLPFC, and posterior parietal lobe regions (Fig. 3c). Important associations were observed between *N*-back performance and neuroactivation levels. Controls were able to perform equally well on both

Table 3 Comparison of performance and reaction time on the 1-back working memory tasks during the fMRI scan between the four study groups

		Group				ANOVA		
Task and (condition)[a]	Response	1. FAS/PFAS Number of responses Mean (SD) N=15	2. SE/AE Number of responses Mean (SD) N=22	3. ND/AE Number of responses Mean (SD) N=20	4. Control Number of responses Mean (SD) N=13	Overall F (p)[e]	Post hoc Duncan[f]	A priori contrast. Linear trend F (p)[g]
1-back task								
Control: 0-back	True-positive[b]	13.3 (1.3)	13.6 (1.1)	13.7 (0.7)	13.8 (0.6)	0.6 (0.65)		1.5 (0.23)
	True-negative[b]	25.7 (0.5)	25.6 (0.9)	25.6 (1.4)	26.0 (0.0)	0.7 (0.57)		0.6 (0.45)
	False-positive	0.3 (0.5)	0.4 (0.9)	0.4 (1.4)	0.0 (0.0)	0.7 (0.57)		0.6 (0.45)
	False-negative	0.4 (0.09)	0.4 (1.1)	0.3 (0.7)	0.2 (0.6)	0.1 (0.93)		0.3 (0.56)
	Reaction time (ms)[c]	734.0 (109.5)	773.3 (112.4)	734.1 (97.2)	695.7 (103.5)	1.5 (0.22)		1.5 (0.22)
Activation: 1-back	True-positive[d]	10.8 (1.2)	10.6 (1.6)	11.3 (1.6)	11.6 (0.6)	1.9 (0.14)		7.2 (0.058)
	True-negative[d]	25.3 (1.8)	26.0 (1.4)	26.6 (0.7)	26.8 (0.4)	4.4 (0.007)	12, 34	11.6 (0.001)
	False-positive	1.6 (1.8)	1.0 (1.4)	0.4 (0.7)	0.2 (0.4)	4.1 (0.01)	12, 234	10.9 (0.002)
	False-negative	2.2 (1.2)	2.4 (1.6)	1.7 (1.6)	1.4 (0.5)	1.9 (0.13)		3.7 (0.058)
	Reaction time (ms)[c]	862.4 (116.9)	845.2 (183.9)	787.5 (101.3)	710.4 (127.4)	3.5 (0.02)	123, 34	9.7 (0.003)

Among subjects with ≥65% correct true-positive and true-negative responses and able to lie still in the scanner

Duncan a multiple comparison range test; commas separate groups with homogeneous means at $p<0.05$, *F f* statistic, *ms* milliseconds, *SD* standard deviation

[a] In the activation condition, subjects were instructed to respond if the stimulus was the same as the stimulus one slide back (1-back) or two slides back (2-back). In the control condition, subjects were instructed to respond if the stimulus was a man's face

[b] There were 14 true-positive and 26 true-negative stimuli in the 0-back control condition

[c] Reaction time for true-positive and false-positive responses

[d] There were 12 true-positive and 28 true-negative stimuli in the *N*-back activation condition

[e] Numerator degrees of freedom=3; denominator *df*=total sample size minus 4

[f] The Duncan range test was presented only when the Overall *F*-test for the ANOVA was statistically significant ($p<0.05$)

[g] Numerator degrees of freedom=1; denominator *df*=total sample size minus 4

Table 4 Comparison of performance and reaction time on the 2-back working memory tasks during the fMRI scan between the four study groups

		Group				ANOVA		
Task and (condition)[a]	Response	1. FAS/PFAS Number of responses Mean (SD) *N*=13	2. SE/AE Number of responses Mean (SD) *N*=18	3. ND/AE Number of responses Mean (SD) *N*=16	4. Control Number of responses Mean (SD) *N*=13	Overall *F* (*p*)[e]	Post hoc Duncan[f]	A priori contrast. Linear trend *F* (*p*)[g]
2-back task								
Control: 0-back	True-positive[b]	13.2 (1.7)	13.6 (0.7)	13.3 (1.9)	14.0 (0.0)	1.0 (0.41)		1.6 (0.21)
	True-negative[b]	25.6 (1.0)	25.6 (1.0)	25.7 (1.3)	26.0 (0.0)	0.6 (0.62)		1.2 (0.28)
	False-positive	0.3 (0.8)	0.4 (1.0)	0.3 (1.3)	0.0 (0.0)	0.6 (0.61)		0.9 (0.35)
	False-negative	0.8 (1.7)	0.4 (0.7)	0.7 (1.9)	0.0 (0.0)	1.0 (0.41)		1.6 (0.21)
	Reaction time (ms)[c]	792.8 (112.9)	836.3 (154.3)	777.3 (90.1)	712.8 (116.0)	2.6 (0.06)		3.9 (0.051)
Activation: 2-back	True-positive[d]	8.2 (2.5)	7.7 (3.0)	10.5 (1.9)	11.5 (1.1)	9.1 (0.000)	12, 34	19.5 (0.000)
	True-negative[d]	24.5 (2.8)	25.7 (0.8)	25.6 (0.9)	26.4 (1.2)	3.5 (0.02)	1, 234	9.3 (0.004)
	False-positive	2.5 (2.8)	1.3 (0.8)	1.4 (0.9)	0.6 (1.2)	3.5 (0.02)	1, 234	9.3 (0.004)
	False-negative	4.6 (2.3)	5.3 (3.0)	2.5 (1.9)	1.5 (1.1)	9.2 (0.000)	12, 34	18.6 (0.000)
	Reaction time (ms)[c]	886.4 (146.5)	970.1 (213.5)	839.3 (122.9)	783.8 (197.4)	3.2 (0.03)	123, 134	4.2 (0.046)

Among subjects with ≥65% correct true-positive and true-negative responses and able to lie still in the scanner

Duncan a multiple comparison range test; commas separate groups with homogeneous means at $p<0.05$, *F f* statistic, *ms* milliseconds, *p* two-tailed *p*-value, *SD* standard deviation

[a] In the activation condition, subjects were instructed to respond if the stimulus was the same as the stimulus one slide back (1-back) or two slides back (2-back). In the control condition, subjects were instructed to respond if the stimulus was a man's face

[b] There were 14 true-positive and 26 true-negative stimuli in the 0-back control condition

[c] Reaction time for true-positive and false-positive responses

[d] There were 12 true-positive and 28 true-negative stimuli in the *N*-back activation condition

[e] Numerator degrees of freedom=3; denominator *df*=total sample size minus 4

[f] The Duncan range test was presented only when the Overall *F*-test for the ANOVA was statistically significant ($p<0.05$)

[g] Numerator degrees of freedom=1; denominator *df*=total sample size minus 4

the 1-back and 2-back conditions (e.g., the mean number of correct responses were comparable on 1-back and 2-back conditions) (Table 5, Fig. 4a), but a significantly higher level of activation (five-fold higher) was observed during the more difficult 2-back activation to 'achieve' this outcome (Table 8, Fig. 4b). In contrast, the subjects in the FAS/PFAS group performed significantly worse on the 2-back condition relative to the 1-back condition (e.g., the mean number of correct responses was significantly lower on the 2-back than the 1-back condition). And, although the level of activation among the FAS/PFAS was higher during the more difficult 2-back task than the 1-back task, it was considerably lower than the 2-back task activation level observed in the Controls and only two-fold higher than the activation level in the FAS/PFAS during the 1-back task.

Table 5 Performance and reaction time compared between the 1-back and 2-back conditions of the working memory task for each study group

Response	Group							
	1. FAS/PFAS		2. SE/AE		3. ND/AE		4. Control	
	N=13		*N*=18		*N*=16		*N*=13	
	Condition		Condition		Condition		Condition	
	2-back versus 1-back[a]		2-back versus 1-back[a]		2-back versus 1-back[a]		2-back versus 1-back[a]	
	Mean difference (SD)	*F* (*p*) (*df* 1, 12)	Mean difference (SD)	*F* (*p*) (*df* 1, 17)	Mean difference (SD)	*F* (*p*) (*df* 1, 15)	Mean difference (SD)	*F* (*p*)(*df* 1, 12)
True-positive	−2.7 (1.9)	25.9 (0.000)	−2.9 (2.7)	20.9 (0.000)	−1.3 (1.9)	7.7 (0.014)	−0.2 (0.9)	.04 (0.55)
True-negative	−1.2 (3.0)	2.0 (0.18)	−0.4 (1.3)	1.5 (.23)	−1.0 (0.8)	24 (0.000)	−0.4 (1.3)	1.2 (0.29)
False-positive	1.3 (3.0)	2.4 (0.15)	0.4 (1.3)	1.5 (0.23)	1.0 (0.8)	24 (0.000)	0.2 (0.9)	1.2 (0.29)
False-negative	2.5 (1.8)	26.8 (0.000)	2.9 (2.7)	20.9 (0.000)	1.3 (1.9)	7.7 (0.014)	0.4 (1.3)	0.4 (0.55)
Reaction time (ms)	57.8 (142.8)	3.0 (0.11)	167.4 (114.4)	38.5 (0.000)	81.1 (97.2)	11.1 (0.004)	73.3 (98.8)	7.2 (0.02)

Among subjects with ≥65% correct true-positive and true-negative responses

df degrees of freedom, *F F* statistic for the repeated measure ANOVA contrast comparing the 1-back condition to the 2-back condition, *p* two-tailed *p*-value, *ms* milliseconds, *SD* standard deviation, *T* paired *t*-test statistic.

[a] Mean and SD of the difference in response or reaction time in the 2-back activation condition minus the response or reaction time in the 1-back activation condition (e.g., subjects in the FAS/PFAS group had on average 2.7 fewer true-positive responses during the activation condition for the more difficult 2-back task, than during the activation task for the less difficult 1-back task)

Discussion

Primary fMRI findings

In summary, 74% of the 81 subjects were able to provide valid fMRI data on both *N*-back tasks, demonstrating that fMRI studies of children with FASD are feasible, albeit challenging. As expected, performance on the 1-back and 2-back conditions decreased significantly as one advanced across the four groups from the Controls to FAS/PFAS. Activation levels decreased significantly on the 2-back task, but not the 1-back task, as one advanced across the four groups from Controls to FAS/PFAS. Decreased BOLD responses during task conditions are thought to reflect decreases in neuronal activation [39]. Controls performed well on both 1-back and 2-back conditions, but showed significantly higher activation during the more difficult 2-back task. The FAS/PFAS group performed significantly more poorly on the 2-back condition relative to the 1-back condition, despite a higher (albeit not statistically significant) activation during 2-back task. The increase in activation from the 1-back task to 2-back task in the FAS/PFAS group, however, was significantly less than the increase observed in the Control group. Of the regions assessed, those with the greatest activity during the *N*-back tasks were the right inferior frontal gyrus, right posterior parietal lobe, right DLPFC, and right middle frontal gyrus. The level of activation during 2-back task in these regions was significantly lower in the FAS/PFAS relative to the Controls, with the SE/AE and ND/AE groups showing levels of activation intermediate to the FAS/PFAS and Controls. When significant contrasts in activation were observed between FAS/PFAS and Controls, the contrasts always involved regions in the right hemisphere. Within each group, reaction times slowed with increasing difficulty

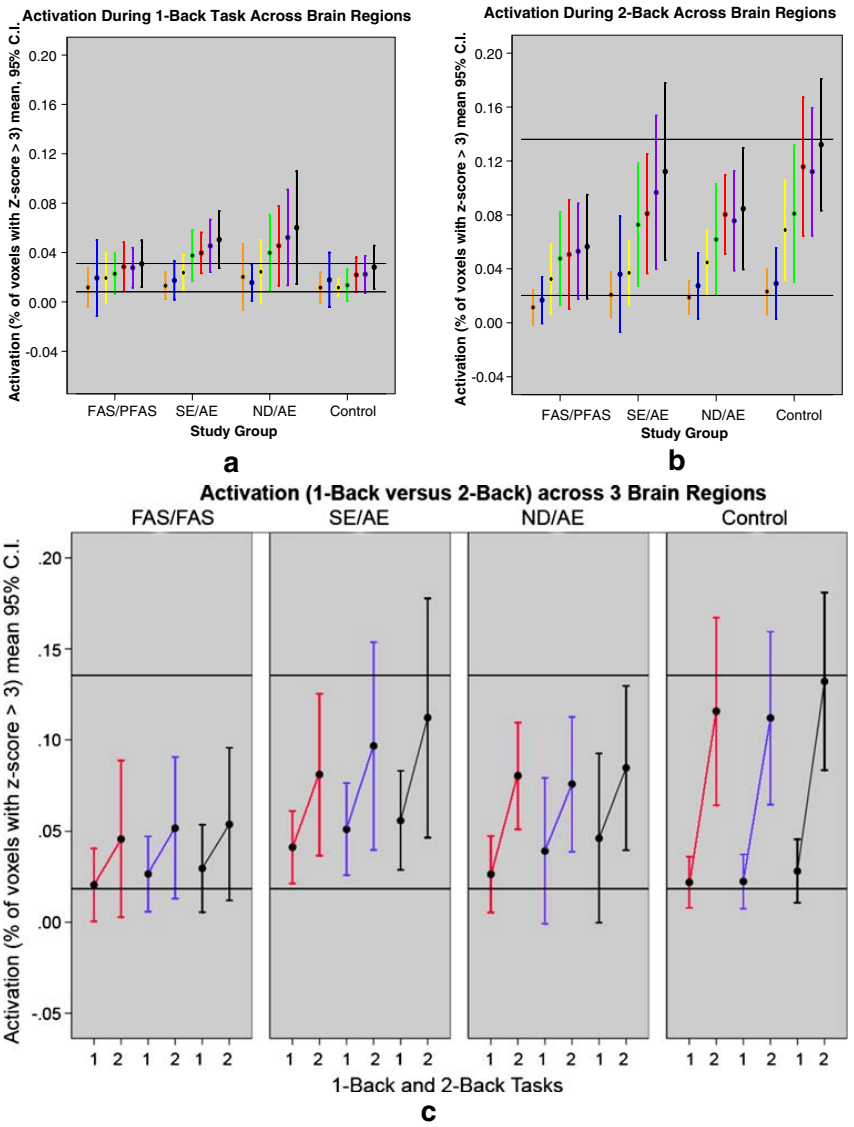

Fig. 3 Activation (mean percent of voxels with *z*-scores>3) in right brain regions **a** 1-back task. **b** 2-back task. **c** 1-back task versus 2-back task for three regions with greatest levels of activation: right middle frontal gyrus, DLPFC, and posterior parietal lobe. Key: Brain regions with valid fMRI data: precentral gyrus (*orange*), anterior cingulate gyrus (*blue*), anterior parietal lobe (*yellow*), inferior frontal gyrus (*green*), posterior parietal lobe (*red*), dorsolateral prefrontal cortex (*purple*), middle frontal gyrus (*black*)

of the task. Across the groups, reaction times were slower in the FASD groups than in the Control group.

All groups in the present study showed comparable activation in the anterior cingulate region, which is involved in affective behaviors, nociception, and executive functions [40]. As summarized by Malisza et al. [16], the activity of this region, which is modulated by task demands and response selection, has been shown to increase during working memory tasks in both children and adults [41–43]. These increases, however, may be more closely linked to the attention demands of working memory tasks, than to the memory demands themselves (which have been associated with DLPFC and parietal activations) [43]. In one of the few FASD-fMRI studies conducted to date (and presented more fully below), Malisza et al. [16] 4 also reported consistent activation in the cingulate region across all subjects in their FASD and Control groups. They speculated that the consistent activity may reflect the fact that participants were paying comparable attention to the task; a conclusion strengthened by the fact that their FASD and Control groups performed comparably on a continuous performance task. The consistent anterior cingulate activity observed across the four study groups in the current study may also reflect that participants in all four groups were

Table 6 Brain activation (mean percent of voxels with activity *z*-scores>3) in regions of interest during the 1-back working memory condition relative to the control condition, across the four study groups

Region: in ascending order of activation		Group				ANOVA		
		1. FAS/PFAS *N*=15 Mean (SD)	2. SE/AE *N*=22 Mean (SD)	3. ND/AE *N*=20 Mean (SD)	4. Control *N*=13 Mean (SD)	Overall *F* (*p*)[a]	Post hoc Duncan[b]	A priori contrast. Linear trend *F* (*p*)[c]
Precentral gyrus	L.	0.006 (0.009)	0.010 (0.013)	0.018 (0.056)	0.006 (0.009)	0.6 (0.64)		0.1 (0.86)
	R.	0.012 (0.028)	0.013 (0.025)	0.020 (0.057)	0.012 (0.020)	0.3 (0.87)		0.1 (0.88)
Anterior cingulate gyrus	L.	0.020 (0.049)	0.028 (0.059)	0.010 (0.016)	0.014 (0.023)	0.6 (0.60)		0.4 (0.48)
	R.	0.019 (0.055)	0.017 (0.035)	0.016 (0.031)	0.012 (0.031)	0.1 (0.99)		0.1 (0.89)
Anterior parietal lobe	L.	0.022 (0.022)	0.025 (0.025)	0.029 (0.067)	0.029 (0.036)	0.1 (0.96)		0.2 (0.63)
	R.	0.019 (0.037)	0.024 (0.033)	0.024 (0.055)	0.012 (0.011)	0.3 (0.79)		0.2 (0.62)
Inferior frontal gyrus	L.	0.027 (0.032)	0.047 (0.046)	0.034 (0.043)	0.029 (0.029)	0.0 (0.98)		0.1 (0.87)
	R.	0.023 (0.029)	0.038 (0.047)	0.039 (0.066)	0.013 (0.021)	1.1 (0.35)		0.2 (0.64)
Posterior parietal lobe	L.	0.032 (0.030)	0.036 (0.031)	0.044 (0.078)	0.039 (0.049)	0.2 (0.92)		0.2 (0.62)
	R.	0.028 (0.036)	0.039 (0.037)	0.045 (0.069)	0.022 (0.023)	0.8 (0.84)		0.1 (0.80)
DLPFC	L.	0.029 (0.029)	0.046 (0.034)	0.039 (0.049)	0.037 (0.037)	0.6 (0.63)		0.1 (0.71)
	R.	0.028 (0.029)	0.045 (0.048)	0.052 (0.083)	0.022 (0.025)	1.1 (0.36)		0.1 (0.89)
Middle frontal gyrus	L.	0.031 (0.031)	0.045 (0.033)	0.043 (0.055)	0.043 (0.044)	0.4 (0.76)		0.5 (0.50)
	R.	0.031 (0.034)	0.050 (0.052)	0.060 (0.029)	0.028 (0.029)	1.0 (0.40)		0.1 (0.98)

Among subjects with ≥65% correct true-positive and true-negative responses
DLPFC dorsolateral prefrontal cortex, *F f* statistic, *L.* left, *p* two-sided *p*-value, *SD* standard deviation, *R* right
[a] Numerator degrees of freedom=3; denominator *df*=total sample size minus 4
[b] The Duncan range test was presented only when the overall *F*-test for the ANOVA was statistically significant ($p<0.05$); commas separate groups with homogeneous means at $p<0.05$
[c] Numerator degrees of freedom=1; denominator *df*=total sample size minus 4

paying comparable attention to the task. Perhaps this is an indication that the method used to identify subjects truly engaged in the tasks (>65% correct true-positive and true-negative responses on the *n*-back tasks) was successful. It is also worth noting that event-related fMRI studies [44, 45] have shown activation in the anterior cingulate associated with error commission and detection. More specifically, Kiehl et al. [45] used event-related fMRI techniques to examine the neural responses to appropriate (correct rejects and correct hits) and inappropriate (errors of commission) behavioral responses during a go/no-go task. Analyses of the inappropriate responses revealed extensive activation in the rostral anterior cingulate cortex and in the left lateral frontal cortex. These areas were not activated for correctly classified trials (correct rejects and correct hits). Although significantly more *N*-back commission errors were observed among the FAS/PFAS group relative to the Controls in the current study, anterior cingulate activation was not higher in the FAS/PFAS group relative to the Controls. Perhaps this reflected an absence of error detection among the FAS/PFAS, which could explain, in part, their poorer performance on *N*-back. When typically developing subjects make an error, their reaction times are typically slower on the subsequent trial [44, 46]. This phenomenon is considered evidence for central error monitoring. When reaction times during correct responses and commission errors were compared between the FAS/PFAS and Control groups in the current study, the children with FAS/PFAS exhibited significantly less slowing of reaction time after commission errors. For Control subjects, the mean reaction time was significantly slower (mean 207, SD 1.2 ms) during commission errors than during correct responses (mean 115, SD 58 m) (paired $t=31.9$, $p=0.03$) in the 2-back condition. In contrast, the FAS/PFAS group had comparable reaction times during commission errors and correct responses (mean 212, SD 64 and mean 183, SD 55 respectively) (paired $t=0.3$, $p=0.80$). This observation further supports that the FAS/PFAS group may not have been detecting their errors.

fMRI and working memory in healthy populations

Research on healthy populations suggest regional activation patterns during working memory tasks that closely mirror the findings in our Control group. The DLPFC, posterior parietal cortex, middle frontal gyrus, and Broca's area are essential in successful working memory performance [41, 47–55]. The middle frontal gyrus is known to be important for ongoing storage and maintenance of information [50, 56, 57], while posterior parietal lobe is seen activated in most working memory tasks with some spatial processing component, and DLPFC is highly activated the greater the

Table 7 Brain activation in regions of interest during the 2-back working memory condition relative to the control condition, across the four study groups

Region		Group				ANOVA		
		1. FAS/PFAS N=13 Mean (SD)	2.SE/AE N=18 Mean (SD)	3.ND/AE N=16 Mean (SD)	4.Control N=13 Mean (SD)	Overall F (p)[a]	Post hoc Duncan[b]	A priori contrast. Linear trend F (p)[c]
Mean percent of voxels with activity z-scores>3								
Precentral gyrus	L.	0.021 (0.04)	0.012 (0.04)	0.016 (0.02)	0.008 (0.01)	0.5 (0.69)		1.1 (0.31)
	R.	0.011 (0.02)	0.021 (0.03)	0.019 (0.02)	0.023 (0.03)	0.5 (0.71)		1.0 (0.32)
Anterior cingulate gyrus	L.	0.012 (0.19)	0.031 (0.09)	0.028 (0.03)	0.047 (0.06)	0.7 (0.54)		1.9 (0.18)
	R.	0.017 (0.03)	0.036 (0.09)	0.028 (0.05)	0.029 (0.04)	0.3 (0.84)		0.2 (0.69)
Anterior parietal lobe	L.	0.043 (0.06)	0.039 (0.04)	0.046 (0.04)	0.080 (0.07)	1.6 (0.19)		3.1 (0.08)
	R.	0.032 (0.04)	0.037 (0.05)	0.045 (0.05)	0.069 (0.06)	1.5 (0.24)		3.7 (0.06)
Inferior frontal gyrus	L.	0.056 (0.08)	0.087 (0.09)	0.068 (0.06)	0.076 (0.06)	0.5 (0.72)		0.2 (0.66)
	R.	0.048 (0.06)	0.073 (0.09)	0.062 (0.08)	0.081 (0.08)	0.4 (0.72)		0.9 (0.37)
Posterior parietal lobe	L.	0.051 (0.07)	0.059 (0.06)	0.065 (0.05)	0.096 (0.07)	1.4 (0.26)		3.5 (0.07)
	R.	0.051 (0.07)	0.081 (0.09)	0.080 (0.06)	0.116 (0.09)	3.1 (0.05)	123, 234	4.4 (0.04)
DLPFC	L.	0.061 (0.08)	0.088 (0.08)	0.083 (0.07)	0.097 (0.06)	0.6 (0.60)		1.4 (0.24)
	R.	0.053 (0.06)	0.097 (0.12)	0.076 (0.07)	0.112 (0.08)	3.2 (0.04)	123, 234	2.2 (0.14)
Middle frontal gyrus	L.	0.064 (0.08)	0.089 (0.08)	0.092 (0.08)	0.112 (0.07)	0.9 (0.46)		2.4 (0.12)
	R.	0.056 (0.06)	0.112 (0.13)	0.085 (0.08)	0.132 (0.08)	3.8 (0.01)	123, 234	2.9 (0.10)
Mean activity z-score across all voxels								
Precentral gyrus	L.	−0.36 (0.73)	−0.70 (0.81)	−0.51 (0.83)	−0.78 (0.51)	0.9 (0.48)		1.3 (0.26)
	R.	−0.37 (0.74)	−0.57 (0.89)	−0.28 (0.84)	−0.23 (0.37)	0.6 (0.59)		0.6 (0.44)
Anterior cingulate gyrus	L.	−0.42 (0.84)	−0.13 (1.07)	−0.34 (0.71)	−0.08 (0.80)	0.5 (0.69)		0.6 (0.45)
	R.	−0.39 (0.73)	−0.25 (1.14)	−0.45 (0.81)	−0.36 (0.72)	0.2 (0.92)		0.0 (0.92)
Anterior parietal lobe	L.	0.04 (0.59)	−0.27 (0.70)	−0.09 (0.66)	0.20 (0.60)	1.4 (0.25)		0.7 (0.41)
	R.	−0.12 (0.66)	−0.43 (0.68)	−0.07 (0.68)	0.17 (0.62)	2.1 (0.11)		2.2 (0.14)
Inferior frontal gyrus	L.	−0.03 (0.49)	0.36 (0.90)	0.09 (0.64)	0.27 (0.71)	0.9 (0.46)		0.5 (0.47)
	R.	−0.01 (0.65)	0.25 (1.04)	0.25 (0.66)	0.50 (0.54)	1.5 (0.23)		2.6 (0.12)
Posterior parietal lobe	L.	0.07 (0.74)	0.02 (0.74)	0.19 (0.51)	0.41 (0.56)	1.1 (0.38)		2.3 (0.13)
	R.	0.02 (0.91)	0.05 (0.86)	0.35 (0.54)	0.65 (0.67)	3.0 (0.04)	123, 34	5.6 (0.02)
DLPFC	L.	0.05 (0.60)	0.40 (0.80)	0.33 (0.59)	0.46 (0.59)	1.0 (0.41)		2.1 (0.16)
	R.	0.03 (0.70)	0.41 (1.08)	0.42 (0.67)	0.74 (0.43)	3.3 (0.03)	123, 234	4.9 (0.03)
Middle frontal gyrus	L.	0.11 (0.75)	0.43 (0.81)	0.48 (0.63)	0.59 (0.59)	1.1 (0.34)		3.0 (0.09)
	R.	0.06 (0.79)	0.51 (1.15)	0.52 (0.77)	0.90 (0.44)	3.9 (0.01)	123, 234	5.8 (0.02)

Among subjects with ≥65% correct true-positive and true-negative responses
DLPFC dorsolateral prefrontal cortex, *F f* statistic, *L.* left, *p* two-tailed *p*-value, *SD* standard deviation, *R* right
[a] Numerator degrees of freedom=3; denominator *df*=total sample size minus 4
[b] The Duncan range test was presented only when the overall *F*-test for the ANOVA was statistically significant ($p<0.05$); commas separate groups with homogeneous means at $p<0.05$
[c] Numerator degrees of freedom=1; denominator *df*=total sample size minus 4

demands of the task [41, 47, 50, 52, 56, 58, 59] Studies have also observed contrasts in right versus left hemisphere activation that appear to be influenced by age and type of task. Positron emission tomography (PET) involving working memory tasks have shown predominantly right hemisphere activation in the frontal cortex [51, 60], posterior parietal cortex, and anterior cingulate [43] of healthy children and young adults, but bilateral activation in older adults [60]. While spatial working memory tasks activate bilaterally, there are key regions (DLPFC and posterior parietal cortex) that have shown activation predominantly in the right-hemisphere [55]. Smith [23] showed object memory activates right DLPFC.

fMRI and working memory in fragile X syndrome

In an fMRI study of visuospatial working memory among children with fragile X syndrome, Kwon et al. [13] observed similar outcomes to the present FASD study. Relative to their comparison group, subjects with fragile X syndrome performed significantly worse on the 2-back task, but not on the 1-back task. In a region-of-interest analysis

Table 8 Increase in brain activation (using the activation measure: mean percent of voxels with activity *z*-scores>3) during more difficult 2-back task compared to 1-back task, across the four study groups

Region		Group							
		1. FAS/PFAS		2. SE/AE		3. ND/AE		4. Control	
		N=12		*N*=18		*N*=16		*N*=13	
		2-back minus 1-back[a]		2-back minus 1-back[a]		2-back minus 1-back[a]		2-back minus 1-back[a]	
		Mean difference (SD)	*F* (*p*) (*df* 1, 11)	Mean difference (SD)	*F* (*p*) (*df* 1, 17)	Mean difference (SD)	*F* (*p*) (*df* 1, 15)	Mean difference (SD)	*F* (*p*) (*df* 1, 12)
Precentral gyrus	L.	0.018 (0.04)	2.0 (0.19)	0.001 (0.04)	0.2 (0.89)	0.012 (0.02)	5.2 (0.04)	0.002 (0.01)	0.3 (0.60)
	R.	0.008 (0.02)	1.6 (0.23)	0.007 (0.04)	0.7 (0.42)	0.009 (0.04)	0.8 (0.40)	0.012 (0.03)	1.9 (0.19)
Anterior cingulate gyrus	L.	0.003 (0.03)	0.2 (0.66)	0.001 (0.03)	0.1 (0.85)	0.022 (0.04)	6.1 (0.03)	0.033 (0.06)	4.0 (0.07)
	R.	0.006 (0.03)	0.4 (0.52)	0.018 (0.05)	2.0 (0.18)	0.019 (0.06)	1.8 (0.20)	0.011 (0.06)	0.5 (0.48)
Anterior parietal lobe	L.	0.013 (0.06)	0.7 (0.43)	0.012 (0.04)	1.5 (0.25)	0.035 (0.05)	7.6 (0.02)	0.050 (0.07)	7.6 (0.01)
	R.	0.014 (0.05)	0.8 (0.38)	0.014 (0.05)	1.6 (0.23)	0.033 (0.06)	4.4 (0.05)	0.057 (0.06)	11.6 (9.005)
Inferior frontal gyrus	L.	0.030 (0.08)	1.8 (0.22)	0.032 (0.09)	2.2 (0.16)	0.051 (0.07)	9.4 (0.01)	0.047 (0.07)	5.5 (0.04)
	R.	0.027 (0.06)	2.3 (0.15)	0.029 (0.07)	2.9 (0.11)	0.034 (0.11)	1.5 (0.25)	0.067 (0.09)	7.5 (0.02)
Posterior parietal lobe	L.	0.016 (0.06)	0.8 (0.39)	0.023 (0.06)	3.1 (0.10)	0.043 (0.07)	5.8 (0.03)	0.057 (0.07)	7.6 (0.02)
	R.	0.025 (0.08)	1.3 (0.28)	0.039 (0.08)	4.6 (0.04)	0.054 (0.08)	6.5 (0.02)	0.094 (0.09)	15.0 (0.002)
DLPFC	L.	0.031 (0.08)	1.9 (0.19)	0.035 (0.08)	3.6 (0.08)	0.058 (0.08)	7.8 (0.01)	0.060 (0.07)	9.8 (0.009)
	R.	0.025 (0.07)	1.8 (0.21)	0.046 (0.09)	4.1 (0.06)	0.036 (0.12)	1.5 (0.25)	0.090 (0.08)	15.7 (0.002)
Middle frontal gyrus	L.	0.032 (0.08)	2.0 (0.19)	0.037 (0.07)	4.5 (0.04)	0.063 (0.10)	6.3 (0.02)	0.069 (0.08)	10.4 (0.007)
	R.	0.024 (0.07)	1.3 (0.28)	0.056 (0.11)	4.4 (0.05)	0.038 (0.14)	1.2 (0.29)	0.081 (0.09)	19.4 (0.001)

Among subjects with ≥65% correct true-positive and true-negative responses

df degrees of freedom, *DLPFC* dorsolateral prefrontal cortex, *F F* statistic for the repeated measure ANOVA contrast comparing activation during 1-back versus 2-back, *L.* left, *p* two-tailed *p*-value, *R* right, *SD* standard deviation

[a] Mean and SD of the difference in the activation level between the 1-back and 2-back tasks

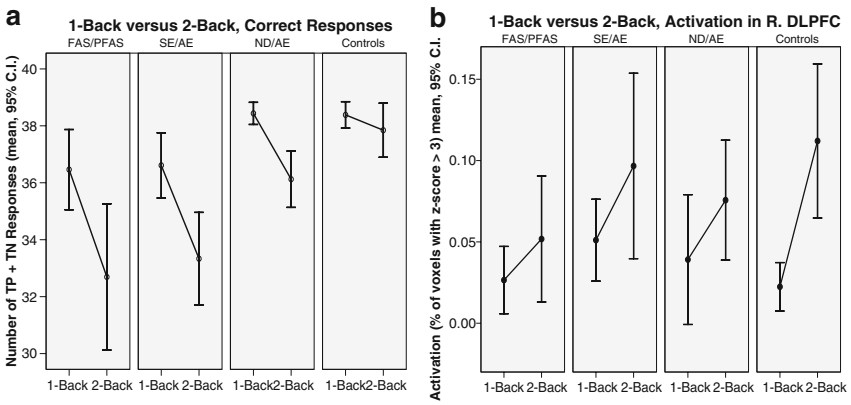

Fig. 4 **a** Mean number of correct (true-positive and true-negative) responses during 1-back versus 2-back conditions across the four groups. **b** Increase in activation (mean percent of voxels with *z*-score>3) during 1-back task versus 2-back task across the four groups in the right dorsolateral prefrontal cortex (*DLPFC*)

focused on the inferior frontal gyrus, middle frontal gyrus, superior parietal lobule, and supramarginal gyrus, comparison subjects showed significantly increased brain activation between the 1-back and 2-back tasks, but subjects with fragile X syndrome showed no change in activation between the two tasks. The investigators concluded that subjects with fragile X syndrome were unable to modulate activation in the prefrontal and parietal cortex in response to an increasing working memory load. They speculated these findings may be explained by a ceiling effect. The subjects with fragile X syndrome may have recruited all of their neuronal resources needed for working memory in the 1-back task. In the 2-back task, the fragile X syndrome group experienced significant deterioration in performance with a lack of coherent recruitment in areas subserving working memory.

It is interesting to note in the current study that during the 1-back task, the FAS/PFAS group exhibited activation levels that were comparable (if not slightly higher) than the Controls, but demonstrated significantly poorer 1-back performance. During the more difficult 2-back task, both activation and performance were significantly lower in the FAS/PFAS group than the Control group. One might speculate that the 1-back outcome reflected 'neural inefficiency' [12, 61], while the 2-back outcome reflected a 'ceiling effect' [13]. What is 'neuronal inefficiency'? Casey [12] postulated in an fMRI study of nonspatial working memory in healthy children, that incomplete myelination may result in poorer conduction efficiency and thus greater energy expenditure. And, in an fMRI study of working memory in girls with and without ADHD, significantly higher activation in the DLPFC was observed among the girls with ADHD, despite comparable working memory performance [61]. The investigators interpreted these findings as evidence of neural inefficiency. In the present FASD study, evidence of significant white matter/myelin deficiencies, and poorer performance despite comparable activation levels were observed in the FAS/PFAS group relative to the Controls. One could postulate that if the requisite neuronal resources for the 1-back task were deficient and/or inefficient in our FAS/PFAS group, comparable activation could have produced inferior performance. When the more difficult 2-back task is encountered, a ceiling effect [13] may have occurred. The Control group demonstrated that a significantly higher level of activation was required to achieve accurate performance on the more difficult 2-back task. The FAS/PFAS group may have been activating all of the neuronal resources they had, but the resources were too deficient, not just inefficient, to achieve comparable activation or performance.

FASD fMRI studies

To our knowledge, only three fMRI-FASD studies have been published to date [14–16]. Marlisza et al. [16] examined fMRI activation patterns corresponding to *N*-back spatial working memory tasks in adults and children with FASD, and in age- and sex-matched Controls. It is important to note their subjects with FASD performed too poorly on the 2-back task to include these findings, so it was dropped from all analyses. To be included in their analyses, all participants had to achieve a minimum of 50% correct responses on the Simple task, and on at least one of the remaining *N*-back tasks (Blank or 1-back). Complete data were available for 23 children (nine FASD, 14 Controls) and 19 adults (ten FASD and nine Controls). Subjects with FASD were diagnosed with FAS, partial FAS, or ARND in accordance with the Canadian FASD diagnostic guidelines [32]. The Canadian diagnostic criteria are near identical to the FASD 4-Digit Diagnostic Code used in the present study. Children with FASD displayed greater inferior-middle frontal lobe activity, while greater superior frontal and parietal lobe activity was observed in Controls. Children in the Control group also showed an overall increase in frontal lobe activity with increasing task difficulty, while children with FASD showed decreased

activity. Adults with FASD demonstrated less functional brain activity overall, but greater inferior middle frontal lobe activity during the simpler tasks, relative to Controls. Adults in the Control group demonstrated greater inferior frontal activity with increasing task difficulty, while this pattern was not consistently observed in adults with FASD. All four groups showed increasing activity with increases in task difficulty in the parietal and frontal regions at more superior slice levels. They concluded their results suggested impairment in spatial working memory in those with FASD that does not improve with age.

Sowel et al. [14] examined fMRI activation patterns corresponding to verbal paired associate learning in a group of 11 children with FASD (two FAS, four PFAS, five Neurobehavioral disorder/alcohol exposed diagnosed with the 2004 FASD 4-Digit Code [27]. Controls included 16 typically developing children with little or no prenatal alcohol exposure (they were excluded if they were prenatally exposed to one drink or more per week, or more than two drinks on any one occasion). Among the children with typical development, prominent activation was observed in the left medial temporal lobe, left dorsal frontal lobe, and bilateral posterior temporal cortices during learning and recall. Analyses revealed significantly less activation in left medial and posterior temporal regions and significantly more activation in right dorsal frontal cortex in the alcohol-exposed children relative to Controls, even when group differences in memory test performance were statistically controlled. The investigators concluded their results may indicate an increased reliance on frontal memory systems, when in the children with heavy prenatal alcohol exposure, perhaps compensating for dysfunctional medial temporal memory systems, when presented with a difficult verbal memory task.

Fryer et al. [15] examined fMRI activation patterns corresponding to a Go/No-Go task in a group of 13 adolescents (8–18 years old) with prenatal alcohol exposure (six FAS and seven without FAS) and nine Controls with no prenatal alcohol exposure. The alcohol-exposed group was evaluated by a dysmorphologist. No FASD diagnostic criteria were cited. The Go/No-Go task is quite different from an *N*-back working memory task, as it requires response inhibition and perhaps involves a lighter working memory load. Mean total brain volume was not significantly different between the alcohol-exposed and Control groups. Interestingly, performance on the go/no-go task was also not significantly different between the alcohol-exposed group and the Control group. During portions of the task that required response inhibition, alcohol-exposed subjects showed greater blood oxygen level-dependent (BOLD) response across prefrontal cortical regions (including the left medial and right middle frontal gyri), while they showed less right caudate nucleus activation, compared to Control subjects. The investigators concluded their results suggest that the frontal–striatal circuitry thought to mediate inhibitory control may be sensitive to alcohol teratogenesis.

Overall, the three FASD fMRI studies report significant differences in brain activation patterns were observed between FASD and Control groups during verbal learning [14], response inhibition [15], and spacial working memory [16] tasks. Significant differences in brain activation patterns were also detected between FASD and Control groups in our study of nonspatial working memory. All of these tasks require higher-order cognitive abilities that are often deficient in individuals with FASD [17–21].

In conclusion, the results of this study demonstrate it is possible (albeit challenging) to use fMRI to study brain activation in children with FASD. This study also shows that children across the full spectrum of FASD exhibit significant working memory deficits. These deficits are correlated with abnormalities in activation in brain areas that are known to be involved in working memory. Alterations in brain activation provide compelling evidence that cognitive and behavioral deficits among individuals with FASD are, to an important extent, "brain-based." An important component of a FASD diagnostic evaluation is confirmation of CNS abnormality. Our ability to detect CNS abnormalities is dependent on the sensitivity of today's measurement tools. These results demonstrate the potential research and diagnostic value of this non-invasive MR tool.

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Interventions for children with fetal alcohol spectrum disorders (FASDs): Overview of findings for five innovative research projects☆

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ABSTRACT

It is well established that prenatal exposure to alcohol causes damage to the developing fetus, resulting in a spectrum of disorders known as fetal alcohol spectrum disorders (FASDs). Although our understanding of the deficits and disturbances associated with FASDs is far from complete, there are consistent findings indicating these are serious, lifelong disabilities—especially when these disabilities result from central nervous system damage. Until recently, information and strategies for interventions specific to individuals with FASDs have been gleaned from interventions used with people with other disabilities and from the practical wisdom gained by parents and clinicians through trial and error or shared through informal networks. Although informative to a limited degree, such interventions have been implemented without being evaluated systematically or scientifically. The purpose of this article is to provide a brief overview of a general intervention framework developed for individuals with FASDs and the methods and general findings of five specific intervention research studies conducted

☆ The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention. The authors would like to thank the participating children and families for their tremendous contribution to each of these studies.

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within this framework. The studies evaluated five different interventions in five diverse locations in the United States, with different segments of the FASD population. Nonetheless, all participants showed improvement in the target behaviors or skills, with four studies achieving statistical significance in treatment outcomes. Important lessons emerged from these five interventions that may explain success: including parent education or training, teaching children specific skills they would usually learn by observation or abstraction, and integration into existing systems of treatment. A major implication of these research studies for families dealing with FASDs is that there are now interventions available that can address their children's needs and that can be presented as scientifically validated and efficacious to intervention agents such as schools, social services, and mental health providers. In the field of FASD research and clinical service, a common theme reported by families has been that clinicians and professionals have been reluctant to diagnose their children because there were no known effective treatments. Results of these five studies dispel that concern by demonstrating several interventions that have been shown to improve the lives of individuals with FASDs and their families.

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It is well established that prenatal exposure to alcohol can damage a developing fetus, resulting in a spectrum of disorders known as fetal alcohol spectrum disorders (FASDs; Jones, Smith, Ulleland, & Streissguth, 1973; Warren et al., 2004). Affected individuals can experience a wide range of negative life long effects, including structural malformations, learning disabilities (including mental retardation), or complex and persistent psychosocial problems. The full spectrum includes diagnoses of fetal alcohol syndrome (FAS), partial FAS (pFAS), alcohol-related neurodevelopmental disorder (ARND), and alcohol-related birth defects (ARBD) (Bertrand et al., 2004; Stratton, Howe, & Battaglia, 1996).

Despite ongoing efforts to prevent alcohol-exposed pregnancies, infants continue to be born with FASDs (Hymbaugh et al., 2002; May & Gossage, 2001; May et al., 2006). FASDs are not as rare as generally thought and studies of particularly vulnerable populations have yielded prevalence estimates that exceed those of other, more widely recognized developmental disabilities. Studies in the United States have reported prevalence rates for the full FAS case definition, ranging from 0.2 to 1.5 cases per 1000 births across various populations (Astley, Stachowiak, Clarren, & Clausen, 2002; Bertrand et al., 2004; May & Gossage, 2001). Prevalence estimates for the entire spectrum range from 3 to 10 times the prevalence of full FAS (Stratton et al., 1996) resulting in thousands of children born affected by prenatal alcohol exposure each year.

As is true for all children with developmental disabilities, access to interventions, especially early interventions, is a protective factor that improves the long-term developmental outlook for those with an FASD (Streissguth, Barr, Kogan, & Bookstein, 1996). Thus, interventions for individuals affected by prenatal alcohol exposure are an important educational and public health need. Despite the troubling number of children with FASDs, information and strategies for interventions specific to this population have been gleaned from interventions used with other disabilities without adaptation and from the practical wisdom gained by parents and clinicians through trial and error or informal networks. In 2001, in response to the Healthy Children Act of 2000, the Centers for Disease Control and Prevention (CDC) provided federal funding to develop systematic, specific, and scientifically evaluated interventions appropriate for children with FASDs and their families. Awards were made to five grantees to develop interventions. All five interventions specifically addressed the neurodevelopmental needs of children with FASDs. The purpose of this article is to provide a brief overview of the

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general framework and procedures for these intervention projects and their central findings. More in-depth descriptions of the methodology and results for each intervention study are addressed in publications elsewhere (Chasnoff et al., submitted for publication; Kable, Coles, & Taddeo, 2007; O'Connor et al., 2006; Olson et al., in preparation).

1. Intervention framework

All of the interventions were designed to improve the developmental outcomes of individuals with FASDs, reduce secondary conditions, and improve the lives of families affected by FASDs. Although our understanding of the deficits and disturbances associated with FASDs is far from complete, individuals exposed to alcohol during fetal development can show evidence of central nervous system (CNS) dysfunction resulting from structural brain damage (Ma et al., 2005; Spadoni, McGee, Fryer, & Riley, 2007). These CNS disabilities can range from subtle to serious, with affected individuals presenting variable combinations of deficits in memory, information processing, academic skills, social skills (including pragmatic language and social communication skills), attention, motor skills, and executive functioning, as well as significant behavioral and mental health issues (Bertrand et al., 2004; Kable & Coles, 2004; O'Connor et al., 2002; Streissguth et al., 1996). Learning and life skills affected by prenatal exposure vary greatly among individuals, depending on the amount of alcohol exposure, the timing and pattern of exposure, and the affected individual's current environmental history (Streissguth, 1997). As a result, the intervention appropriate for an individual with an FASD and his or her family vary according these factors.

Grantees were requested to incorporate three common components in their intervention trials: (a) interventions targeting a specific area of deficit or risk among the study population (rather than entering into a single, collaborative intervention to be implemented by all sites), (b) provide children in both treatment and control groups with multidisciplinary assessments that guided referrals for standard care as indicated (e.g., speech therapy), and (c) incorporate specific instruction and training for parents and caregivers regarding basic information about FASDs, advocacy skills, and caregiver support. Across sites, specific interventions focused on math skills, behavioral regulation, peer relations and social communication, executive functioning, compliance, learning readiness, and challenging behaviors of clinical concern.

2. Human subjects approval

All studies were approved by the CDC Institutional Review Board (IRB) and by the individual IRBs from each research site. For children under state guardianship, the IRB of the applicable state Department of Children and Family Services reviewed and approved the research. Informed consent was obtained from the parent(s) or legal guardian(s), and assent was obtained from children at appropriate ages for each intervention.

3. Diagnosis of participants across intervention sites

Participants for all interventions were recruited from established FASDs and genetics clinics. Every child received a multidisciplinary evaluation by trained clinicians to assess for the presence of the diagnostic features of an FASD. Children with any of the diagnoses within the spectrum were eligible. Two of the study sites (University of California at Los Angeles and University of Washington) used the *Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code* (Astley, 2004). This system uses a 4-digit diagnostic code reflecting the magnitude of expression of four key diagnostic features of fetal alcohol syndrome (1) growth deficiency; (2) the FAS facial phenotype, including short palpebral fissures, flat philtrum, and thin upper lip; (3) CNS dysfunction; and (4) gestational alcohol exposure.

Two sites (Children's Research Triangle and University of Oklahoma Health Sciences Center) used a modified system adapted from the IOM (Stratton et al., 1996) and incorporated aspects of the 4-digit diagnostic code to assess severity of features. One site (Marcus Institute) used Pedscore, a weighted pediatric dysmorphia checklist (Fernhoff, Smith, & Falek, 1980) that has been demonstrated to

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Table 1
Baseline participant characteristics for each intervention research site.

Characteristic	Intervention research site				
	University of California at Los Angeles ($N = 100$)	Marcus Institute ($N = 61$)	Children's Research Triangle ($N = 78$)	University of Oklahoma Health Sciences Center ($N = 58$)	University of Washington ($N = 52$)
Ethnicity (%)					
White, non-Hispanic	54.0	57.4	37.2	39.1	50.0
Black or African American	17.0	38.4	42.3	23.9	25.9
Child sex: males (%)	51.0	60.7	67.9	60.0	51.9
Child age in years (M, SD)	8.59 (1.56)	6.38 (2.00)	8.73 (1.55)	4.70 (1.4)	8.06 (2.07)
Child composite IQ on K-Bit (M, SD)	97.24 (14.83)	81.08 (13.4)	89.79 (16.11)	87.90 (11.20)	94.3 (12.50)
Primary caregiver education (years)	16.28 (0.26)	12.84 (1.4)	14.41 (2.51)	13.90 (2.73)	14.47 (2.26)
Living with biological mother (%)	21.0	1.7	NA	1.1	13.4
Fetal alcohol syndrome (%)[a]	12.0	6.6	14.1	4.6	7.7

[a] FAS diagnosis based on criteria from *Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis*, 2004

accurately reflect common features associated with the diagnosis of an FASD. The Pedscore is the sum of the 30 weighted items on a standard pediatric dysmorphia checklist used to identify alcohol-related dysmorphic features. This checklist is a modification of the usual "genetics" checklist, upon which characteristics associated with the disorder are listed and weighted based on their saliency for the diagnosis (e.g., hypoplastic philtrum is a "3" on a 0–3 scale). The total dysmorphia score obtained is the sum of the 30 weighted items. Pedscores greater than 10 are assumed to indicate a clinically significant degree of alcohol-related dysmorphology. This score is then used with other criteria to diagnose children according to the IOM system (Stratton et al., 1996).

To provide consistency for comparison across sites, all sites re-categorized their participants according to the 2004 guidelines published by the National Taskforce on Fetal Alcohol Syndrome and Fetal Alcohol Effects (NTFASFAE), presented in Table 1. These guidelines address only the full FAS diagnosis. A diagnosis of FAS is applied if: (a) a child demonstrates all three cardinal facial dysmorphic features (small palpebral fissures, smooth philtrum, and thin vermillion border); (b) has prenatal or postnatal growth below the 10th percentile for height or weight; and (c) demonstrates structural, neurological or functional CNS deficits (Bertrand et al., 2004). A confirmed history of prenatal alcohol exposure is a qualifier of the diagnosis, but not a prerequisite according these guidelines.

4. Study 1. Project bruin buddies: a social skills training program to improve peer friendships for children with fetal alcohol spectrum disorders (University of California at Los Angeles)

This study was designed to examine the effect of parent-assisted children's friendship training (CFT) (Frankel & Myatt, 2003) compared with the effect of delayed treatment control (DTC) on the social skills of children with a history of prenatal alcohol exposure, and to examine the maintenance of social skills gained over a 3-month period.

Research suggests that children with FASDs exhibit considerable social impairment. Problems understanding social cues, indiscriminant social behavior, and difficulty communicating in social contexts have been reported among this population (Streissguth, 1997). Both caregivers and teachers have rated children with prenatal exposure to alcohol as having poorer social skills than unexposed children, even after controlling for differences in cognitive functioning (Roebuck, Mattson, & Riley, 1999; Whaley, O'Connor, & Gunderson, 2001). Furthermore, studies of adolescents and adults with FASDs have indicated that social skills deficits continue into adulthood (Carmichael-Olson, Feldman, Streissguth, Sampson, & Bookstein, 1998). Given the high percentage of individuals with prenatal exposure to alcohol, who have significant social problems as they grow older, it is important to intervene early to promote adequate social problem solving and competence.

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The procedure used in this study and all its social skills components were based on the developmental psychology literature pertaining to children's friendships, had been validated empirically, and had been successfully implemented for children 6–12 years of age in multiple clinical contexts and with children having a variety of developmental and psychiatric disorders (Frankel, 2005; Frankel & Myatt, 2003). The procedure included parents as facilitators of their children's social skill performance, which has proven to be a highly successful component of social skills training (Frankel, 2005; Ladd, Profilet, & Hart, 1992). The procedure was modified with specific treatment adaptations to account for the neurocognitive deficits common among children with FASDs. Modifications made primarily involved augmentation in how the treatment was delivered, rather than changes in the content or components of the intervention, thus, preserving the basic integrity of the treatment. Skills taught included: (a) social network formation with the aid of the, (b) informational interchange with peers leading to a common-ground activity, (c) entry into a group of children already in play, (d) in-home play dates, and (e) conflict avoidance and negotiation. Skills were taught didactically through instruction on simple rules of social behavior; modeling, rehearsal, and performance feedback during treatment sessions; rehearsal at home; homework assignments; and coaching by parents during play between children.

4.1. Method

4.1.1. Participants

A total of 183 children 6–12 years of age were assessed for eligibility in the study. Of that number, 83 were excluded for not meeting inclusion criteria ($N = 63$) or failing to keep evaluation appointment ($N = 20$). Of the remaining 100 children, 96 completed the study with 4 families failing to complete the study (2 during intervention and 2 during the delayed treatment waiting period). Sample participants had to have had measurable social skills deficits (≥ -1 standard deviation below the mean) on the socialization domain of the Vineland Adaptive Behavior Scales (VABS; Sparrow, Balla, & Cicchetti, 1984), and a verbal IQ of ≥ 70 on the Kaufman Brief Intelligence Test (K-BIT; Kaufman & Kaufman, 1990). Sample characteristics are presented in Table 1.

4.1.2. Measures and procedures

A two-group CFT or DTC longitudinal design was used. Each consecutive set of 14–16 eligible children formed a cohort. The children within a cohort were assigned, in alternating sequence, to one of the two study conditions (7–8 children in each condition), with an attempt to equate groups on sex and ethnicity. The CFT group received 12 sessions, 90 min in length, delivered over the course of 12 weeks. Parents attended separate concurrent sessions in which they received education on the issues related to FASDs and were instructed on key social skills being taught to their children. On completion of the 12-week intervention, participants in the CFT condition were administered a post-treatment assessment. Children in the DTC condition, for whom treatment had been delayed, then received the CFT. After completing treatment, the DTC participants were then assessed. At the same time, the CFT group completed a 3-month follow-up assessment.

Children and parents were assessed prior to CFT or DTC training, 12 weeks later, and then again at 3 month's follow-up. Children's understanding of the rules of social behavior was measured using the Test of Social Skills Knowledge (TSSK; Frankel, 1994), which is a 17-item forced–choice, criterion-based measure. This measure and similar measures have been used successfully in evaluating treatment gains in other studies of social skills training (Frankel & Myatt, 2003; Pfiffner & McBurnett, 1997). Scores range from 0 to 17, with a higher score reflecting higher social skills knowledge.

Social skill performance was evaluated with the Social Skills Rating System Parent Form (SSRS-P) (Gresham & Elliott, 1990). The SSRS-P is comprised of two scales: Social Skills and Problem Behaviors, presented as standard scores ($M = 100$; $SD = 15$). The Social Skills scale measures cooperation, assertion, responsibility, and self-control. Lower scores represent poorer social functioning. The Problem Behaviors scale measures internalizing, externalizing, and hyperactivity. Higher scores represent greater problem behaviors. The SSRS-P has high criterion-related validity, correlating significantly with other established measures of child social and problem behaviors.

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The Test of Parent Knowledge of FASDs, a project-developed questionnaire in a true/false, forced-choice format, was used to assess parental knowledge about the neurodevelopmental effects associated with prenatal alcohol exposure and of parent advocacy opportunities.

Following treatment, parents were queried regarding their satisfaction with the intervention using the Parent Satisfaction Questionnaire, a project-developed measure consisting of questions rated on a Likert scale with values ranging from negative to neutral to positive.

4.2. Results

Chi-square and independent *t*-tests revealed no statistically significant differences at baseline between the CFT and DTC conditions on demographic variables. To examine the effect of social skills training on children with FASDs, a two-condition (CFT, DTC) ANCOVA design was used. Analyses were conducted on the scores derived from the TSSK completed by the children and on the scores on the SSRS-P completed by the parents. The post-treatment score was the dependent variable and the baseline score was used as a covariate to control for initial levels. After controlling for covariates, children in the CFT group showed statistically significant improvement in their knowledge of appropriate social behavior compared with children in the DTC group (prior to their receipt of the social skills training, $p < .0001$). According to parent report, similar results also were obtained in increasing actual social skills ($p < .03$) and in decreasing problem behaviors ($p < .05$). To examine the maintenance of social skills over a 3-month period following treatment, data from children in the CFT condition were analyzed using two-tailed pairwise *t*-tests. The DTC group received treatment during this time period so they could not be used as a comparison group. Change scores on the TSSK and the SSRS-P from baseline to 3 month's follow-up constituted the dependent variables. Results indicated that children's social skills knowledge, improvement in social skills, and decrease in problem behaviors were maintained over the 3-month follow-up period. Importantly, social skills improved significantly from post-treatment to 3 month's follow-up ($p < .002$), suggesting that children were continuing to benefit from the intervention targeting social skills performance. Similar gains were reported for the children in the DTC group following treatment with CFT.

Results from questionnaires on parent knowledge about prenatal alcohol exposure and parent satisfaction revealed that, following treatment, parents in both groups reported more knowledge about their children's conditions and a high level of satisfaction with the intervention. More than 85% of parents reported that the approach to treating their children's social skills problems was appropriate and 89.2% said they would recommend the training to a friend or relative. Regarding the information that they learned in the sessions, 92.5% of parents reported that the information was useful to them.

4.3. Discussion and conclusions

This study was the first systematic evaluation of a treatment for improving the social functioning of children with FASDs. As such, it represents a promising intervention for these children, who experience multiple failures in social interaction leading to poor peer choices and, for some, juvenile delinquency (Schonfels, Mattson, & Riley (2005)). However, the treatment was performed in a highly controlled university setting. Thus, the next step in determining its effectiveness would be to test the treatment among children enrolling in more typical community-based programs. Given the high rates of mental health problems among children with FASDs (Streissguth et al., 1996; Streissguth & O'Malley, 2000), these children are likely to be seen for treatment in such community settings. Providing increased access to interventions that have been demonstrated empirically to be efficacious with this population is a critical step toward reducing some of the devastating secondary disabilities faced by children with FASDs and in helping their families facilitate change.

5. Study 2. Georgia-sociocognitive habilitation using the math interactive learning experience (MILE) program (Marcus Institute)

This project was developed to evaluate the effect of a sociocognitive habilitation program designed to improve the behavioral and mathematical functioning of alcohol-affected children. Deficits in

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mathematical functioning have been reported consistently among alcohol-affected individuals (Coles et al., 1991; Goldschmidt, Richardson, Stoffer, Geva, & Day, 1996; Howell, Lynch, Platzman, Smith, & Coles, 2006; Jacobson et al., 2003; Mattson, Riley, Gramling, Delis, & Jones, 1998; Streissguth et al., 1996) and have been demonstrated throughout the lifespan of these individuals (Kopera-Frye, Dehaene, & Streissguth, 1996). Poor myelinization, particularly in areas affecting the cross-hemispheric transfer of information (Ma et al., 2005; Wozniak et al., 2006) and altered development and functioning of parietal regions of the brain that are involved in the visual-spatial processing of information (Dehaene, 1997; Geary, 1993) have been posited as potential reasons for the relative deficit in mathematics skills seen among alcohol-affected children.

A psychoeducational program for alcohol-affected children that provided learning strategies to compensate for core alcohol-related neurodevelopmental deficits was developed to facilitate mathematics learning. The program included intensive, short-term individual instruction of each child, as well as training for the child's caregivers and teachers. The goal was to provide a consistent method of instruction of mathematical concepts across therapeutic, home, and school environments. Most clinically referred children have problematic medical and caregiving histories, as well as socioeconomic problems and behavior problems that must be taken into account in designing intervention studies (Kalberg & Buckley, 2007; Kable & Coles, 2004). Therefore, support – which included caregiver education, case management services, and psychiatric consultations, as needed – also was incorporated to allow the child to achieve *readiness to learn*.

Program developers hypothesized that the learning readiness components of the intervention program would increase parental knowledge, would be viewed as helpful, and would result in improved parental perception of behavior. It also was hypothesized that children randomly assigned to a targeted habilitative program to facilitate their mathematical development would demonstrate greater maturation in mathematics skills compared with children who received standard psychoeducational services.

5.1. Method

5.1.1. Participants

Children 3–10 years of age who had a clinical diagnosis of FAS or pFAS were recruited from the Atlanta metropolitan area. Participants were required to have been with their current caregiver for at least 6 months prior to enrollment and to be projected to remain with that same caregiver for the next 6 months. Participants were excluded if their cognitive functioning was in the moderately intellectually deficient range or below, or if they had other serious mental health problems that might have interfered with their ability to benefit from academic instruction. Children who had a dual diagnosis of an FASD and attention deficit disorder were not excluded from participation. A total of 87 participants consented and were enrolled in the study, but only 61 completed study requirements for randomization. Of these, 56 completed post-testing. The mathematics group had two participants drop out and the psychoeducational only group had three families who failed to return for post-testing. Sample characteristics are presented in Table 1.

5.1.2. Measures and procedures

5.1.2.1. Readiness to learn. To establish readiness to learn among participants, case management and psychiatric consultation were provided as needed. Caregivers of participants also were required to attend two training workshops. The first workshop educated parents about FAS and provided information about special education and methods for advocating for their children. The second provided training in how to build positive behavioral regulation skills among children. Parents were given informational manuals elaborating workshop content to use as a reference.

5.1.2.2. Mathematics intervention overview. After caregivers completed the workshops, participants were randomly assigned to either the mathematics intervention group or a standard psychoeducational treatment only contrast group. All participants received the standard psychoeducational treatment consisting of a comprehensive neurodevelopmental evaluation, assistance with educational placement,

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and development of an individualized educational plan within the context of their home school. In addition to the standard psychoeducational services, those in the mathematics intervention group received 6 weeks of tutoring services. Caregivers in the mathematics intervention group also received instruction in supporting mathematics learning at home and weekly home assignments to complement the individualized tutoring sessions. The staff special educator also met with the participant child's teacher to discuss the alcohol-related neurodevelopmental problems the participant had and the individualized educational goals for the program.

The mathematics instructional component of this program was called the math interactive learning experience (MILE). The program incorporated an active learning approach to instruction that was adapted from the "plan-do-review" methodology developed by the High-Scope Perry Preschool Project and was found to have positive long-term consequences on academic achievement and educational attainment (Luster & McAdoo, 1996; Weikart & Schweinhart, 1992) among high-risk children and to be beneficial in cognitive rehabilitation programs for children with acquired brain damage (Ylvisaker et al., 2007).

Children and caregivers in the mathematics intervention group were evaluated prior to participating in the group workshops and within 4 weeks of completing the tutoring program. To control for time between assessments, a participant child from the standard psychoeducational only group was assessed in the same week as a participant child from the mathematics intervention group. Children were evaluated by a psychologist or psychology trainee who was blind to group status.

5.1.2.3. Satisfaction. Following the workshops, caregiver satisfaction for both groups was assessed using Likert scale responses to questions regarding their experiences with the specific treatment components and interactions with staff members.

5.1.2.4. Treatment and FAS knowledge. Caregiver knowledge was assessed for both groups also. Assessed areas included the neurodevelopmental compromises associated with prenatal exposure to alcohol, the specific challenges to learning presented by these difficulties, and behavioral regulation principles. Questionnaires used multiple choice formats.

5.1.2.5. Behavioral outcomes. To measure caregiver experience of children's behavior, the Child Behavior Checklist (CBCL: Achenbach & Rescorla, 2001a, 2001b) was administered at pre-test and post-test to caregivers in both groups.

5.1.2.6. Academic outcomes. All children were administered the *Test of Early Mathematical Ability*, 2nd edition (TEMA-2; Ginsburg & Baroody, 1990) and selected mathematics-related subtests from the *Bracken Early Concept Scales–Revised* (Bracken, 1998). For children 5 years of age or older, the *Key Math-R/NU* (Connolly, 2001) also was administered. For children younger than 5 years of age, developmental testing of premathematics concepts was done using items from the *Bayley Scales of Infant Development*, 2nd edition (Bayley, 1993). Finally, the quality of number writing was assessed by rating the child's number writing for order, orientation, neatness, consistency, and general recognizability using an instrument developed as part of this study (Coles, Kable, Dent, & Lee, 2004).

5.2. Results

Analyses were conducted of the 56 participants who completed post-testing using a two-condition ($N = 29$ mathematics intervention; $N = 27$ psychoeducation only) MANOVA design. Caregiver satisfaction with workshops was very high, with over 90% of caregivers in both study groups agreeing that trainers were knowledgeable and materials were easy to understand and helpful. Pre-test and post-test score differences revealed significant gains in knowledge of FASDs, advocacy topics ($p < .05$), and behavioral regulation ($p < .000$). At post-testing, caregivers also reported fewer problem behaviors on the CBCL ($p < .000$).

Because of the passage of time and the fact that students in both groups were receiving mathematics instruction in school, it was predicted that both groups of children would demonstrate gains in mathematics knowledge, but significantly higher gains would be observed for children in the

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group receiving direct mathematics instruction. This prediction was confirmed: 58.6% of those in the mathematics treatment group demonstrated a gain of over one standard deviation on any of the four mathematics outcome measures used, while only 23.1% of those in the psychoeducation only group did so ($p < .008$).

5.3. Discussion and conclusions

Study results suggested that parent-training components of the program were well received and were associated with reports of improved behavior at post-testing. Although it was possible that these findings might have been temporary or the result of experimenter or participant expectation, they did suggest that educational interventions might be helpful for caregivers and might lead to positive behavioral changes for children. Additional research is needed to further assess the clinical efficacy of the parent training components of this intervention. This study used only a pre-test/post-test design and not a control group with random assignment to evaluate the effect of the workshop, as was done to evaluate the mathematics intervention component.

The results of the mathematics intervention component suggested that a targeted psychoeducational program that addresses the alcohol-related neurodevelopmental difficulties might help to remediate deficits associated with prenatal alcohol exposure. Although the program was relatively short in duration, participants in the mathematics treatment group were more likely to have made a clinically significant gain than were participants assigned to the standard psychoeducational intervention group, providing evidence that effective teaching methods can improve learning for alcohol-affected children.

6. Study 3. Neurocognitive habilitation for children with fetal alcohol spectrum disorders (Children's Research Triangle)

The specific aim of this study was to develop and evaluate a program of neurocognitive habilitation for children who had been in foster care or who had been adopted, and who had a diagnosis of FAS or ARND. In 1998, the U.S. General Accounting Office (1998) reported that 74% of children in foster care in Illinois had at least one parent who was required to undergo drug or alcohol treatment as part of the case plan for family reunification. In about half the cases, alcohol was used alone or in combination with illegal drugs such as cocaine or heroin, and almost all of the children had been prenatally exposed. The pervasiveness of alcohol involvement in these cases indicated that children in foster care were a group of children at very high risk of an FASD. Even children who eventually were adopted, still had foster care as part of their developmental history (Astley et al., 2002; Streissguth et al., 1996). Unfortunately, the very factors that protect children with FASDs from developing secondary disabilities are the ones that children in the child welfare system frequently lack, such as being raised in a stable, nurturing home; being diagnosed before 6 years of age; having no sexual or physical abuse history; not changing households every few years; not living in a poor quality home; and receiving early intervention services (Streissguth et al., 1996). Thus, children with FASDs and their families need interventions tailored to their foster care experiences, and which can provide skills that mitigate negative experiences as well as counteract any lack of protective factors.

The neurocognitive habilitation program was developed to be a systematic intervention strategy for children in the child welfare system that had a diagnosis of FAS or ARND. The program provided education and support to enhance the families' capabilities to care for the children, and focuses on improving the children's executive functioning, a central deficit for children with FASDs (Mattson et al., 1998; Rasmussen, 2005). The intervention strategies developed for the program focused on the concept that children would be best equipped to improve their executive functioning deficits if they were better able to self-regulate. The program curriculum combined self-regulation techniques and strategies with tools for improving executive functioning skill sets: memory, cause and effect reasoning, sequencing, planning, and problem solving.

Many of the concepts for improving self-regulation that were used in the neurocognitive habilitation program curriculum were adapted from the *Alert Program*© (Williams & Shellenberger, 1996). The *Alert Program*© uses the metaphor of a car engine to describe the concept of self-regulation. Children are told that their brains are like a car's engine and can make their bodies run in high-, low-, or just-right gear. The

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program is broken down into three stages: teaching children engine speed identification skills, offering children a variety of strategies to change their engine speeds to desired speed states, and learning to monitor sensorimotor input to regulate their state of arousal.

6.1. Method

6.1.1. Participants

A total of 78 foster and adopted children, 6–11 years 11 months of age, who had a confirmed history of prenatal alcohol exposure were recruited to participate in the study. Consents for participation were signed by the foster or adoptive parent(s) and, as appropriate, the Office of the Guardian of the Illinois Department of Children and Family Services (DCFS). Four children, all assigned to the treatment group, were eliminated from the sample because they and their parents did not participate in at least 4 of the 12 treatment sessions and did not follow through for exit and follow-up evaluations. These four children (three males, 1 female) did not differ from other children enrolled in the study or from other children assigned to the treatment group.

The Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000) is a questionnaire that assesses executive function behaviors in home and school environments. The BRIEF's internal consistency and test–retest reliability have been demonstrated to be adequate, while convergent and discriminant validity have been demonstrated with other measures of inattention, impulsivity, learning skill, and emotional and behavioral functioning.

The Roberts Apperception Test for Children (RATC) (McArthur & Roberts, 1982) is designed for children and adolescents 6–15 years of age to assess their perceptions of common interpersonal situations. Children's responses are scored on standardized scales measuring adaptive and maladaptive functioning (eight adaptive scales and five clinical scales) and providing *t* scores. The RATC scoring system has shown adequate interrater agreement and split-half reliability estimates have shown reasonable consistency. The validity of the RATC has been demonstrated in multiple ways (McArthur & Roberts, 1982.).

6.1.2. Measures and procedures

A total of 90 children and their families qualified for the study and were invited to participate; 12 declined because of geographical issues. From the 78 children who were enrolled in the study, 2 cohorts were developed via random table assignment after initial intake and a general treatment plan had been completed. The children in the intervention group ($N = 40$) received a full evaluation at Children's Research Triangle and participated in a course of 12 weekly 75-min neurocognitive habilitation group therapy sessions based on the *Alert Program*© (Williams & Shellenberger, 1996), while their parent(s) concurrently participated in a parent education group. The intervention lasted for 12 weekly sessions.

Control group children ($N = 38$) received a full evaluation at Children's Research Triangle, but were referred for services such as occupational therapy, physical therapy, or speech and language therapy through existing community- and school-based agencies, the community standard for service access and delivery at the time of the study. In contrast to children in the intervention group, children and their families in the control group did not participate in neurocognitive habilitation group therapy.

Children were enrolled in cohorts and, as much as possible, the intervention children were divided by chronological and developmental levels, with an optimal group size of five children. Licensed clinical psychologists and post-doctoral fellows under the direct supervision of a licensed psychologist conducted the assessments. Therapy services were provided by licensed clinical psychologists, licensed clinical social workers, and pre- and post-doctoral students under the direct supervision of a licensed psychologist. Outcome measures (BRIEF and RATC) were administered during the post-intervention period (following the approximately 12 weeks of intervention services) and after a comparable delay for children in the control group.

6.2. Results

Of the 40 families in the intervention group who began treatment, 4 were not able to complete the intervention or post-testing. None of the families in the control group were lost to follow-up. Because

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the research design was a repeated measures design, a double multivariate analysis of variance approach to the data analysis–which is an extension of profile analysis–was used. The multiple subscales of a measure are considered a profile and three major questions must be addressed about this profile: (a) *Do different groups have parallel profiles* (parallelism question)? (b) *Does one group, on average, score higher on the combined subscales than another* (levels question)? and (c) *Are all the subscales the same at each time point of measurement* (flatness question)? In each analysis, all three of these questions were tested.

6.2.1. Brief

The multivariate omnibus test of significance that tested the effect of the treatment over time on the BRIEF was statistically significant ($p = .006$). Because the BRIEF has eight subtests, we conducted follow-up tests (Roy–Bargmann stepdown *F*-tests) to try to understand exactly how the treatment and control groups differed. There were no differences between the groups on any single subtest that were pronounced enough to reach statistical significance. These results suggest that the significant effect seen between the groups would be best understood as a combination of the subtests. That is, no single subtest independently would account for more of the variance between groups than any other subtest.

6.2.2. RATC

The multivariate omnibus test of significance that tested the effect of the treatment over time on the RATC adaptive scales was statistically significant ($p = .012$). There are eight adaptive scales, so again we conducted follow-up tests. One subtest did have a substantial difference that reached significance ($p < .01$): the Resolution 1 scale was the subscale that differentiated between the treatment and control groups. It appeared that children in the control group tended to narrate stories with more ease and identify unrealistic solutions to problems.

6.3. Discussion and conclusions

The results of this study suggested that children who participated in the neurocognitive habilitation program demonstrated significant improvement in executive functioning skills compared with the children in the control group. Because the treatment approach focused on the concept that children's self-regulatory problems contribute to executive functioning difficulties, the result suggested that the self-regulatory strategies and techniques taught to the children were beneficial from the parents' perspective; children appeared to learn the regulatory strategies and techniques taught in group and, as a result, parents saw improvements in the children's executive functioning skills.

The children in the treatment group at outcome also differed from those in the control group in their response to a projective storytelling test on the RATC: children in the treatment group told fewer stories that had unrealistic solutions to problems. This result might seem less intuitive than the first because the treatment approach clearly did not address directly storytelling or developing realistic solutions to stories specifically. However, one plausible explanation for this result would be related to the content of the groups. One component of the therapy focused on sequencing skills and cause-and-effect thinking. Thus, it was possible that the children internalized these concepts, as demonstrated through projective stories that had fewer unrealistic endings.

The results of this study suggested that the neurocognitive habilitation program is a promising approach to help foster and adopted children with FASDs improve their self-regulation and executive functioning skills. Further refinement of this curriculum and further investigation is needed to establish the treatment efficacy of this program.

7. Study 4. Parent–child interaction therapy: application of an evidence-based treatment to reduce behavior problems among children with fetal alcohol spectrum disorders (University of Oklahoma Health Sciences Center)

The aim of the study was to evaluate two group-based interventions for children with FASDs) that would reduce (a) behavior problems among children with FASDs and (b) decrease parenting stress

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among caregivers. One treatment used a group adaptation of an evidenced-based behavioral parent training treatment, Parent-Child Interaction Therapy (PCIT) (Eyberg & Boggs, 1998) that provided both parents and children with a live, coached practice of behavioral parenting skills. The other was a parent-only Parenting Support and Management (PSM) program that comprised components from other effective behavioral programs (Barkley, 1997; Webster-Stratton, 2001).

Behavior difficulties are significant secondary disabilities among very young children with prenatal exposure to alcohol and other substances (Streissguth et al., 1996). According to research, caregivers' perceptions of children with prenatal exposure to alcohol and other drugs are more negative than those of children without exposure due to ongoing behavior problems that do not respond to traditional parenting (Griffith, Azuma, & Chasnoff, 1994; Paley, O'Connor, Frankel, & Marquardt, 2006). Furthermore, both biological and foster mothers of children with prenatal substance exposure have reported higher levels of parenting stress than have caregivers of children without prenatal exposure (Griffith et al., 1994). The difficult behaviors often seen among the children with FASDs together with the caregivers' negative perceptions and stress often have a detrimental impact on the child's development. Effective intervention programs to address the behavior problems of very young children with an FASD, and the distress experienced by caregivers, are essential for the overall well-being of the children and their caregivers (Bertrand et al., 2004; Streissguth et al., 1996).

Behavioral parent training is considered the single most effective method for ameliorating significant externalizing behavior problems among children in general (Brestan & Eyberg, 1998; Brinkmeyer & Eyberg, 2003). PCIT is an empirically supported intervention consisting of behavioral parent training to effect significant behavior change by the child. PCIT seeks to enhance the parent–child relationship, increase appropriate social skills, reduce inappropriate behaviors, and institute a positive discipline program (Eyberg & Boggs, 1998). PCIT is a short-term intervention, typically lasting 12–16 sessions. Decreases in conduct problems and noncompliant behaviors, as well as improvements in a child's self-esteem, have been found for those who complete PCIT (Eisenstadt, Eyberg, McNeil, Newcomb, & Funderburk, 1993). Although PCIT focuses on the parent–child relationship, research has found generalization of the positive effects to daycare, preschool, and elementary school settings (McNeil, Eyberg, Eisenstadt, Newcomb, & Funderburk, 1991).

A caveat is that behavioral parent training programs such as PCIT presume that disruptive childhood behavior originates in parent–child interaction patterns that inadvertently condition and reinforce disruptive behavior and create a negative parent–child relationship. However, the origin of the behavior problems for children with FASD are most likely rooted in the brain damage caused by prenatal exposure to alcohol. Thus the general PCIT intervention needs to be adapted to accommodate specific parenting skills that work within the learning and behavior skills of the child with an FASD who has brain damage.

7.1. Methods

7.1.1. Participants

A total of 58 children 3–7 years of age with an FASD and their caregivers were recruited for participation in this study. The FASD diagnosis was made by a clinical geneticist using a modified IOM criterion after a clinical dymorphia and CNS evaluation. Children participating had to have cognitive functioning at ≥30 months as measured by the *Bayley Scales of Infant Development*-second edition (Bayley, 1993) or the *Wechsler Preschool and Primary Scales of Intelligence*-third edition (WPPSI-III; Wechsler, 2002). Caregivers had to have an IQ of ≥65 on the K-BIT (Kaufman & Kaufman, 1990) to obtain reasonable comprehension of self-report measures. Sample characteristics are presented in Table 1. Of the 58 children recruited for the study, 46 entered treatment and were randomized.

7.1.2. Measures and procedures

The project used a randomized two-group longitudinal design. A blocked randomization pattern was used to ensure that both intervention conditions had equivalent proportions of biological versus nonbiological parents and equivalent proportions of male and female children. Following a comprehensive developmental and genetics evaluation to ascertain that FASD inclusion criteria were met, all families received a basic education/advocacy service prior to the parenting intervention.

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Participant in both treatment and comparison conditions received 14 weeks of the assigned intervention (PCIT or PSM), with each weekly session lasting 90 min. Measures of child disruptive behavior problems and parenting stress were collected at each weekly treatment visit. A larger test-battery of measures was collected at baseline, mid-treatment, and treatment completion.

The PCIT intervention caregivers and children both were seen for treatment. Families were seen with their children for all but 2 of the 14 weekly sessions. Those two sessions focused on behavior education in general to orient families to the concept of behavior changes. In the remaining sessions, skills taught to the caregivers were practiced in session with their child with in vivo coaching via a one-way mirror and listening device placed in the parent's ear (bug-in-the-ear). Parent–child interactions were scored (coded) prior to treatment in order to assess areas most in need of intervention, as well as to establish a baseline of parent–child interaction pattern. At each of the sessions, an assessment of skills was obtained to focus the session in a family-specific manner. Families were provided feedback after each session regarding their progress in acquiring targeted skills and homework between sessions. They moved through the intervention based on skill acquisition.

The comparison program for this study also had a group format for parents only, intended to represent a plausibly beneficial but less costly and intensive intervention that could be easier to implement in community settings. It incorporated elements and approaches adapted from other supported behavioral programs shown to reduce behavior problems among children (Barkley, 1997; Webster-Stratton, 2001). The components included psychoeducation about development among children with an FASD, then moved families from awareness through acceptance and then to action, including ideas such as behavioral contracts and star charts. Discussions of implementation, challenges, and problem solving were part of each session with the group participants.

Prior to beginning the intervention, all parents completed a series of questionnaires. These included the *Parenting Stress Index third edition-Short Form* (PSI; Abidin, 1995), the Eyberg Child Behavior Inventory (ECBI; Eyberg & Pincus, 1999), and the CBCL. All of these measures have strong psychometric properties. An observation of parent–child interactions was completed and rated using the *Dyadic Parent–Child Interaction Coding System-II* (DPICS-II; Eyberg & Robinson, 2002) (presented elsewhere). The PSI and ECBI were completed each week. The ECBI shows good treatment sensitivity, such that any change is due to intervention rather than passage of time. All measures were administered again at the completion of treatment and at follow-up appointments.

7.2. Results

Approximately half (46%) of families in the study completed the entire 14-week treatment program (50% for PCIT, 42% for PSM). In general, an attrition rate of 50–75% has been reported for children referred for treatment associated with externalizing behavior problems (Brinkmeyer & Eyberg, 2003), so the observed rates were well within that range. Group differences in attrition were examined using a simple nonparametric survival analysis. This approach allows examination of dropout events and hazard rates across time. Group differences did not approach statistical significance and the survival and hazard functions visually appeared quite similar. Qualitative surveys of reasons for dropout were examined and, most often, dropout was reported to have little to do with the intervention and more to do with life circumstances (e.g., military deployment, serious illness, surgery, death in the family, removal of child from home, and job conflicts). The average number of sessions completed was 9.14 for the PCIT group and 8.92 for the PSM group.

Weekly PSI and ECBI measures were analyzed using growth models. Models for each of the two ECBI scale scores (Intensity and Problem scales) and the overall PSI score were executed. Each model treated intercepts and slopes as random effects and included tests for group differences in intercepts and slopes. Significant time (session) effects were observed for the PSI ($p < .05$), the ECBI Intensity score ($p < .001$) and the ECBI Problem score ($p < .001$). All effects were in the direction of significant reductions in scores across time. Group comparisons of time slopes (i.e., improvement rates) did not reach statistical significance for any of the three tests, although there was a nonsignificant trend favoring PCIT for the PSI ($p = .14$).

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To estimate prescores and postscores from the growth models, estimated marginal means were generated for the pretime and posttime points. For children in the PCIT group, the mean EBCI pre-test standard score was 65, with a mean standard score of 58 post-test. For the PSM group on this measure, the mean pre-test standard score was 63, with a mean standard score of 57 post-test. Mean ECBI scores were in the clinically significant for both groups at baseline. At post-treatment, mean scores for both groups had dropped below clinical cutoffs. Examining variance components of the growth model suggested that there was very little case-to-case variation in rates of improvement across sessions.

For parents in the PCIT group, the mean PSI pre-test standard score was 97, with a mean standard score of 84 post-test. For the PSM group parents, on the PSI, the mean pre-test standard score was 88, with a mean standard score of 85 post-test.

7.3. Discussion and conclusions

Improvement over time was noted across outcome measures and across intervention conditions. No statistically significant differences in improvement between the two randomized intervention conditions were observed. Significant overall improvement in parent distress over time was noted across participants, and there were nonsignificant trends for group PCIT to yield somewhat greater rates of improvement. Child behavior problems also improved over time for both groups at rates that did not differ. Because the study did not include a placebo or no-treatment condition, spontaneous improvement, regression toward the mean or measurement artifact cannot be ruled out as explanations for improvement over time. Nonetheless, it is more likely that the improvements were to some extent the result of the interventions rather than simply the passage of time. As the measure of behavior problems, the ECBI has been found to be stable over timeframes comparable with those in this study, with change usually noted only in response to effective intervention (Eyberg & Pincus, 1999). Furthermore, research related to children with FASDs who have behavior difficulties in the significant range (as these children presented), generally do not show decreases in problems with time (Streissguth et al., 1996).

This study also found promise for reduction in behavior problems using a simple and easily implemented parent-only support and education intervention—PSM. This format might prove more cost effective in working with families with children with FASDs, given that it would require less effort and cost to deploy. Parents in both intervention programs were satisfied with treatment. All PCIT parents reported feeling positive about the program, and indicated that they would recommend it to a friend or relative. All parents enrolled in the PSM group also reported feeling positive about the program, and 80% indicated that they would recommend PSM to a friend or relative. In terms of behavioral change, 100% of PCIT parents felt that their presenting problems had improved, while 70% of PSM parents reported improvement. All parents felt neutral or confident that their child could manage future behavior problems using the skills from their respective programs. No significant differences in mean overall satisfaction were seen between groups.

In sum, the study generally supported both intervention models as viable alternatives for caregivers of children with FASDs, which was encouraging. Clear improvement can be observed using even brief behavioral interventions, using different types and intensities of behavioral interventions, even within the context of limited intervention dose and retention. This was particularly encouraging given that behavior problems among children with FASDs are generally viewed as strongly neurologically involved and not simply the product of parent–child interaction patterns.

A few limitations and corresponding directions for future research should be considered. First, the study sample was small and precluded examining potentially important case factors that might have suggested a differential benefit for one intervention model over the other. For example, it is possible that group differences might have existed depending on the initial level of a child's disruptive behavior or the parent's distress. Second, not all potentially important outcomes were examined. For example, it would have been important to learn whether the improvements noted on parent-report measures would translate to school or other environments. The nonsignificant trend favoring PCIT for reducing parent stress needs to be examined in a study with greater statistical power (i.e., having a larger sample size).

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8. Study 5. Families moving forward: a behavioral consultation intervention to improve outcomes for families raising children with fetal alcohol spectrum disorders (University of Washington)

The overall goal of this study was to evaluate an intervention designed to improve caregiver self-efficacy, meet family needs, and reduce child problem behaviors. The specific aims of the study were: (a) to create a feasible, specialized behavioral consultation intervention – the Families Moving Forward (FMF) Program – for caregivers raising children with FASDs, based in part on positive behavior support techniques, and (b) to assess the efficacy of the FMF intervention, when compared with the community standard of care, using a randomized control trial design.

Most children with FASDs are identified in elementary school—a pivotal time when neurodevelopmental deficits and problematic, often disruptive behavior commonly emerge among children with prenatal alcohol exposure. What can be called "challenging behavior" is an important issue for this child population. In clinical data for 861 school-aged children referred to an FASD diagnostic clinic network in Washington State, a striking 82% showed a variety of behavior and learning problems. Parents raising children with FASDs often are highly stressed by these children (Paley et al., 2006) and these families have many unmet intervention and resource needs (Olson, Brooks, Davis, & Astley, 2004). Clinical experience and wisdom in the field suggest these parents struggle to attain positive parenting attitudes, find and use effective parenting skills, acquire needed specialized knowledge, and make effective linkages to appropriate school and community resources (Olson, Jirikowic, Kartin, & Astley, 2007).

Developmental systems literature and natural history research on individuals with FASDs has identified a cluster of factors describing a nurturing, appropriately structured, stable caregiving environment in childhood as an important protective influence for positive outcome (Streissguth et al., 2004). Translation of these concepts into tailored, useful, family-focused, scientifically validated parenting and behavior management intervention methods for use by clinicians is an important next step. Interventions are needed especially for use with caregivers raising children with FASDs who in the preschool and school years already show challenging behaviors of clinical concern, with inevitable signs of family and school disruption. Parenting intervention methods must be flexible enough to apply to the very diverse group of birth, foster, kinship, and adoptive families who raise children with FASDs. Intervention methods must also respond to the often complex psychosocial histories and circumstances of these children.

The FMF model was designed to modify specific parenting attitudes and parenting responses toward their child's problem behaviors. Through changed caregiving, the ultimate aim of FMF services was to reduce clinically concerning child problem behavior and improve other outcomes during the school years. The newly developed FMF model of behavioral consultation integrated several empirically supported child management and parent training techniques—and the clinical wisdom of "what works" in the field of FASDs (Kalberg & Buckley, 2007; Kleinfeld & Westcott, 1993; Streissguth, 1997). Most centrally, clinicians using the FMF intervention teach caregivers the skills involved in a "parent-friendly" positive behavior support approach to dealing with challenging child behaviors (called "brainstorming"). Developed in 2002, this approach is based on social learning theory and is congruent with evolving literatures on developmental disabilities and traumatic brain injury (e.g., Hieneman, Childs, & Sergay, 2006; Koegel, Koegel, & Dunlap, 1996; Lucyshyn, Dunlap, & Albin, 2002; O'Neill et al., 1997; Schoenbrodt, 2001; Ylvisaker et al., 2007). The FMF model simplifies and organizes the positive behavior support approach to make it systematic and usable for parents and clinicians. In the FMF intervention model, there is a strong emphasis on helping parents to learn and use antecedent-based behavior strategies, as well as on how to create and advocate for "accommodations" (modifications of the physical or caregiving environment) for their child. Clinicians using the FMF intervention assist caregivers in altering cognitions and attitudes, most centrally "reframing" their understanding of the behavior of the child with FASDs as affected by neurodevelopmental disabilities rather than as willful disobedience. The FMF intervention is hypothesized to improve parenting self-efficacy; meet family needs; reduce child-related stress; lead to other beneficial changes in parenting knowledge and behavior; and, ultimately, reduce "challenging" child disruptive behavior.

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8.1. Methods

8.1.1. Participants

A sample of 52 children 5–11 years of age and their caregivers were enrolled from the Washington State FAS Diagnostic and Prevention Network (FAS DPN) of diagnostic clinics. Child participants all had measurable externalizing or attention problems, or both, of clinical concern at enrollment using an age-appropriate version of the CBCL (Achenbach and Rescorla, 2001b). All had evidence of variable but clear neuropsychological impairment and marked adaptive function problems seen in comprehensive test results across multiple developmental domains, yet were high-functioning enough to show a verbal IQ of $\geq$70 (and a group mean score well within the average range) on the K-BIT. There were other inclusion and exclusion criteria (e.g., living within driving distance of the University of Washington and no history of head injuries.). This sample was carefully selected to focus on children with FASDs who had demonstrated significant challenging behaviors at a young age, and were those most likely to show later costly secondary disabilities. See Table 1 for sample demographics.

8.1.2. Measures and procedures

A study was conducted using a stratified, randomized block design to assign families to either the FMF intervention group or to the community standard of care group, balanced on race or ethnicity, child sex, and birth or non-birth parent family structure. The community standard of care group received any of a range of services currently available in Washington State, which is a relatively well-served geographic area. This was a conservative intent-to-treat study design, so all participants enrolled in treatment were included in the analysis regardless of treatment dose received. Analyses revealed groups (each with $N = 26$) were well-matched on these variables, and on child age, alcohol-related diagnosis at enrollment, cumulative postnatal risk, and caregiver education.

The FMF intervention is a feasible, low-intensity, sustained model of supportive behavioral consultation lasting 9–11 months, with at least 16 every-other-week sessions typically lasting 90 min each. Services are carried out by mental health providers who receive affordable, specialized training to carry out the intervention. Limited and focused consultation with school staff and, when appropriate, community providers are available. This is an "added value" intervention, so FMF participation does not preclude families or children from receiving medication or other community services. In fact, interventionists also try to link families to needed resources in the community. The FMF intervention is manualized into a "flow" of sessions, but is also individualized for different families. There is a curriculum of easily readable, brief written materials to select from and use in sessions easily obtainable from the FMF training office. Checklists, now computerized, completed by providers after each session allow efficient monitoring of intervention fidelity. Interventionists have access to a supervisor, resource information from an FASD family advocacy group, and, if needed, brief expert consultation from a psychologist or occupational therapist, or both. In this initial efficacy trial, FMF services were provided in families' homes, but the intervention model was developed to be flexible enough for use in a variety of clinical settings.

The FMF intervention was newly developed, so some outcome measures were created for the study; and multiple aspects of sample characteristics, treatment process, and treatment outcome were examined. Primary outcomes discussed here include change from baseline to follow-up on: (a) parenting attitudes of efficacy and child-related stress as measured by the Parenting Sense of Competence (PSOC) Efficacy Scale score (Johnston & Mash, 1989); (b) stress levels as measured by the PSI Child Domain score (Abidin, 1995); and (c) caregiver ratings of child disruptive behavior immediately post-intervention as assessed by the ECBI Problem score (Eyberg & Pincus, 1999). Also discussed here are group differences at follow-up on: (a) perceived family needs met (a measure developed for this study assessing satisfaction with support received from child- and family-focused services) (family needs met, average of applicable needs met); (b) self-reported rating of change in parental self-care across the intervention period (a measure developed for the study); and (c) caregiver ratings of satisfaction with provider skill in caring for children with special health care needs using the Multidimensional Assessment of Parental Satisfaction (MAPS) score (Ireys & Perry, 1999). Results reported here were gathered immediately post-treatment, unless otherwise noted (e.g., PSI). The PSOC, ECBI, PSI, and MAPS all have very adequate psychometric properties.

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8.2. Results

One hundred percent of children and 96% of caregivers completed baseline and follow-up assessments across both study groups. Of the 26 families enrolled in an intervention, 96% completed the full 9–11-month treatment (with one of the families completing a simplified intervention retaining all basic features of the model). Analyses were based on all 52 children (FMF group, $N = 26$; community standard group, $N = 26$).

Compared with caregivers in the community standard of care group, from baseline to follow-up, caregivers participating in the FMF intervention showed a significantly improved sense of parenting self-efficacy immediately post-treatment. A greater percentage of caregivers parents in the FMF intervention group reported engaging in more self-care behaviors than parents in the community comparison group (72% versus 44%, respectively; $p < .05$). No group differences emerged for change in child-related parenting stress, which was not surprising given the ongoing, marked executive functioning, other language and learning deficits or low adaptive function of these children.

A highly significant group difference ($p < .01$) revealed that the FMF intervention group reported their family needs were met more often than did the comparison families. In addition, provider satisfaction was significantly higher among those in the intervention group. On average, parents receiving the intervention also reported FMF services as highly acceptable (mean of 6.51 overall on averaged 7-point scales, where 7 is the highest score), and that they had received "just the right amount" of services for their child and themselves. Intervention was delivered with good fidelity.

Findings of perceived child behavior change were also observed. Caregivers receiving FMF services reported immediately after treatment that their children with FASDs showed a significantly decreased number of challenging disruptive behavior problems. On the ECBI, a parent report measure, children in the FMF intervention group achieved a mean standard score of 66.88 at pre-test, clearly in the clinical range. At post-test, these children showed a mean standard score of 60.54—a score just above the cutoff between the borderline clinical range and what is considered within normal limits. Among those in the community comparison group, scores at baseline and follow-up indicated clinical concern about child behavior, with the mean ECBI pre-test standard score at 64.38 and the mean post-test standard score at 63.20. The group difference was statistically significant ($p < .05$). Child behavior change over time, correlates of positive outcome, and group differences in parenting knowledge and behavior change will be discussed in future publications.

8.3. Discussion and conclusions

Children with FASDs and clinically concerning behavior problems, especially disruptive behavior and attention problems, place a heavy burden on caregivers at home and at school, and often come to the attention of mental health providers (Fryer, McGee, Matt, Riley, & Mattson, 2007; O'Connor et al., 2002; Streissguth & O'Malley, 2000). Preschool and school-aged children already struggling with clinically concerning behaviors are likely at highest risk for secondary disabilities in daily function later in life, which will require services that increase societal costs. The FMF model appears to provide a feasible, satisfying intervention with promising efficacy tailored to this high-priority group of children with FASDs and their caregivers. Data from this controlled study so far indicate a positive effect on parenting attitudes and headway on reducing child disruptive behaviors. More efficacy research is needed. Now under way in programmatic research is a project designed to streamline and transition the FMF training program and intervention from its use in a university setting to use by providers in a community setting. The current research will further assess FMF intervention feasibility and efficacy, examine program costs, ensure the FMF training program and intervention model are affordable, and make this scientifically validated intervention more widely available to families in need.

9. General discussion

Until now, information and strategies for interventions specific to individuals with FASDs have been gleaned from work with children having other disabilities (without appropriate adaptation) and

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the practical wisdom gained by parents and clinicians through trial and error. Although informative to a limited degree, such evolving treatments have been implemented without systematic or scientific evaluation. The five interventions presented here are the first specifically designed and adapted for children with an FASD that have been scientifically tested.

These five diverse interventions uncovered basic ingredients that seem important to their success with individuals who have an FASD. Importantly, parent education or training was built into the general framework guiding all the studies. In two (Washington and Oklahoma) studies direct parent training was the primary intervention being assessed. In all studies, parents or caregivers showed improved knowledge about FASDs and applicable parenting issues. Also important was that a primary technique utilized was explicit instruction of the children (California, Georgia, and Illinois). That is, children with an FASD demonstrate a good capacity to learn new skills yet, because of underlying neurological impairment, must do so through explicit instruction rather than through observation and a process of abstracting rules, skills, and knowledge from ongoing situations as do children who are developing typically. Even those interventions focused on parent training included some amount of information on the efficacy of explicit instruction when working with their child with an FASD.

These five studies represent the wide range of possible treatments for children with cognitive, behavioral, or social problems resulting from prenatal alcohol exposure. It is essential to use programmatic research to develop multiple interventions that address the wide range of potential deficits associated with the FASD population. This approach to developing appropriate interventions is important because, as a group, children with FASDs are very heterogeneous in the nature and severity of their problems. The services needed for individuals with FASDs and their families vary according to differing neurological insults, the age or level of maturation of the child, the health or functioning of the family (see Streissguth, 1997; Streissguth et al., 1996), and the overall environment in which the child is living.

Another vital finding across the five reported interventions was that the individualized and targeted interventions specific to deficits among children with an FASD can be implemented within a framework of current community services typically available. Each project worked with already available resources such as special education, therapy services, or counseling to integrate value-added interventions specific to individuals with FASDs. As a result, these scientifically validated intervention projects moved the field forward within a community services context, rather than duplicating already available services.

As with any set of research projects, strengths and weakness were identified. Inclusion of parents as active participants and collaborators in the intervention process, either by direct intervention or adjunct parent training, was a tremendous strength of these research projects. Finally, these projects all benefited from the collaborative nature of the overall research consortium. The consortium allowed individual researchers to recognize problems common across all sites (e.g., recruitment or retention problems) and share solutions.

Intervention research is always a challenge with inherent weaknesses. First and foremost, these interventions were time-limited by funding constraints. A clear need remains to address the long-term effects and follow-up of each intervention. Whether children retained specific skills and knowledge beyond the intervention and follow-up periods could not be addressed in these studies. Further children's ability to generalize newly acquired skills could not be addressed either. For example, although they might learn a math skill or executive functioning technique appropriate for their current age, it is critical to know whether they retain that information as they enter the next developmental or academic stage. It is also important to know whether, once a skill is acquired within one domain, children are able to apply that skill to another domain. For example, if a child masters the skill of adjusting his or her readiness to learn through behavioral regulation techniques to complete mathematics assignments, will he or she be able to apply that skill to other assignments (such as writing) without specific instruction. Finally, because the overall population of children with FASDs is limited, the sample sizes in these studies were limited, although sufficient to demonstrate statistically significant effects. Thus, replication of these studies will be necessary to more solidly establish the reliability of the findings and strengthen their demonstrated effectiveness.

A major implication of these research studies for families dealing with FASDs is that they now have available tested interventions that can address their children's needs and that can be presented as

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scientifically validated and efficacious to intervention agents such as schools, social services, or mental health providers. A common theme reported by families is that clinicians and professionals have been reluctant to diagnose their children because there were no known effective treatments. Results of these five studies clearly dispel that concern. An important next step includes each site partnering with a community agency to adapt its intervention program to the resources, infrastructure, and personnel of its community partner agency.

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PROFILE OF THE FIRST 1,400 PATIENTS RECEIVING DIAGNOSTIC EVALUATIONS FOR FETAL ALCOHOL SPECTRUM DISORDER AT THE WASHINGTON STATE FETAL ALCOHOL SYNDROME DIAGNOSTIC & PREVENTION NETWORK

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ABSTRACT

Background
An interdisciplinary approach to fetal alcohol spectrum disorder (FASD) diagnosis using rigorously defined diagnostic guidelines has been adopted as best practice. Diagnostic clinics are being established worldwide. If these clinics are to successfully compete for limited health care dollars, it is essential to document their value.

Objective
The primary objectives were to document the value of the largest and longest standing interdisciplinary FASD diagnostic program; the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network (WA FAS DPN). Now in its 17th year of operation, the WA FAS DPN is a statewide network of diagnostic clinics all using the 4-Digit Diagnostic Code and contributing to a centralized electronic database.

Methods
The clinical database was used to generate comprehensive profiles of all patients evaluated for FASD from 1993-2005. These profiles were used to answer a multitude of clinical, research, and public health questions including: What is the demand for FASD diagnostic services, who is referred to the clinics, and what are their FASD diagnostic outcomes? Can FAS/D prevalence estimates from this clinical population be used to estimate FAS/D prevalence estimates in the general population? Do FASD diagnostic outcomes vary by race, age or alcohol exposure? Does the presence of other adverse exposures/events lead to more severe outcomes? Does this approach to diagnosis meet the needs of families?

Results
Demand for diagnosis remains very high. Of 1,400 patients (newborn to adult) with confirmed prenatal alcohol exposure, 11% were diagnosed with FAS/PFAS, 28% with static encephalopathy, 52% with neurobehavioral disorder, and 9% with no evidence of CNS abnormality. FASD outcomes varied significantly by age, race, gender, alcohol exposure, and presence of other risk factors. Families reported high satisfaction with the diagnostic process, and receipt of information/services they were unable to obtain elsewhere.

Conclusions
This report documents the immense contribution of a statewide FASD diagnostic program, and underscores the extraordinary value of a comprehensive FASD clinical dataset.

Key Words: *Fetal Alcohol Spectrum Disorders (FASD), FASD 4-Digit Diagnostic Code*

The Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network (WA FAS DPN) is a network of statewide, fetal alcohol spectrum disorder (FASD) diagnostic clinics linked by the core clinical/research/training clinic located at the Center on Human Development and Disability at the University of Washington (UW) in Seattle

Washington. The FAS DPN began as a single CDC-sponsored clinic at the University of Washington in 1993 in response to a national request for proposals for FASD prevention. The philosophy behind the UW proposal was…If you build a clinical diagnostic program that meets the needs of the families raising children with FASD, they would seek out the services of the clinic. In so doing, each time you identified (diagnosed) a child with FAS/D, you had an opportunity to identify and potentially intervene with a woman at high risk for bearing subsequent children with FAS/D (the child's birth mother). The results of that FASD primary prevention effort are presented in Astley et al.[1,2] When the UW FAS DPN clinic first opened in 1993, it was the first to introduce an interdisciplinary approach to FASD diagnosis.[3] The interdisciplinary team included a medical doctor, two psychologists, a speech-language pathologist, an occupational therapist, a social worker, and a family advocate. A gestalt[4] approach to FASD diagnosis was initially used, reflecting the most current guidelines available at the time. This gestalt approach was replaced in 1995 by a more rigorous, case-defined FASD diagnostic system (the FASD 4-Digit Diagnostic Code[5-8]) developed by the UW FAS DPN. The 4-Digit Code was formally released to the public in 1997, with updates in 1999 and 2004. During the first two years of operation, the single UW FASDPN clinic was overwhelmed by demand for FASD diagnostic services, far exceeding its capacity. In 1995, the Washington Chapter of the National March of Dimes provided funding to establish two satellite FASD clinics in two large cities just north (Everett) and south (Federal Way) of Seattle. In 1995, the state legislature through Senate Bill SB5688 mandated further expansion of the program to six satellite clinics (located in Everett, Federal Way, Tacoma, Yakima, Pullman, and Spokane) linked by the core UW clinic in Seattle, establishing the WA FAS DPN.[9] The WA FAS DPN is now in its 17th year of funding support from the state.

The mission of the WA FAS DPN is FASD prevention through FASD screening, diagnosis, intervention, research, and training. To this end, the WA FAS DPN has created a myriad of diagnostic tools, training programs, and screening programs (FASD 4-Digit Diagnostic Code and Lip-Philtrum Guides[5-8] (1997,1999,2004), FAS Facial Analysis Software[10-12] (2003); Foster Care FAS Screening Program[13,14](1999); FASD 4-Digit Code Online Training Course[15](2004)), all of which are available to clinical professionals free or at cost to maximize access. Over the decades, this interdisciplinary approach to FASD diagnosis using the FASD 4-Digit Code has been adopted worldwide.

The core mission of the FAS DPN has always been the advancement of the field through translational research (the rapid translation of clinical research into practice). The foundation of translational research is data management. From the FAS DPN's first day of operation in 1993, all data from the diagnostic clinics have been methodically collected and entered into an electronic clinical/research database with patient consent and Human Subjects Review Board approval. Over the years, this dataset has grown to over 8,000 cases, each with up to 2,000 fields of information, providing a comprehensive documentation of statewide demand for FASD evaluations and extensive detail on the antecedents and outcomes of these evaluations. This dataset supported the development of the diagnostic tools, screening programs, and training programs listed above, and serves as one of the largest research registries of individuals with FASD (n = 2,000) for enrollment into research studies that directly benefit individuals with FASD and their families.[16-25]

Over the years, the clinical field of FASD has come to adopt, as best practice, an interdisciplinary approach to FASD diagnosis using more rigorous, case-defined diagnostic guidelines.[6,7,26,27] Interdisciplinary FASD diagnostic clinics are being established worldwide. If these clinics are to successfully compete for limited health care dollars, it is essential to document their value. To demonstrate the extraordinary and unique value of a statewide interdisciplinary FASD diagnostic clinical program (and the essential role of data collection), the outcomes of the first 13 years of operation of the WA FAS DPN are presented below. The primary objectives of this study were to:

1. Construct a comprehensive profile (based on factors A-K below) of all 1,400 Washington State residents who obtained an FASD diagnostic evaluation at one of seven

WA FAS DPN clinics between 1993 and 2005.

2. Divide the clinical population into four FASD diagnostic subgroups (ranging from no adverse outcomes to severe adverse outcomes), construct a comprehensive profile of each subgroup (based on factors A-K below), and identify risk and protective factors that differentiate the four groups.

Factors

A. Sociodemographics
B. Birth mother and birth father characteristics
C. Growth
D. FAS facial features
E. CNS structural, neurological, and functional outcomes
F. Patient's behavioral profile: Summary of Caregiver Interview and Child Behavior Check List
G. Prenatal alcohol exposure
H. Other prenatal and postnatal risk factors
I. Prevalence of other syndromes
J. Prevalence of mental health disorders
K. Patient satisfaction with the FASD diagnostic process and access to intervention services.

Primary objectives 1 and 2 allow a multitude of clinical, research, and public health questions to be addressed. For example, if a statewide FASD diagnostic program is built, what is the demand for services, who is referred to the clinics, and what are their FASD diagnostic outcomes? Are there individuals with prenatal alcohol exposure who present with no evidence of adverse outcome? Can FAS/D prevalence estimates from the clinical population be used to estimate FAS/D prevalence estimates in the general population? Do FASD diagnostic outcomes vary by race, age, or level of prenatal alcohol exposure? What is the prevalence of mental health disorders and other syndromes in this patient population? Does the presence of other adverse exposures/events (e.g., prenatal exposure to illicit drugs, poor prenatal care, multiple home placements, physical/sexual abuse) lead to more severe dysfunction? Growth deficiency has always been a hallmark of FAS/D. How prevalent is growth deficiency in this patient population? The FASD literature suggests that infants and adults are less likely to present with the full FAS facial phenotype than school-aged children? Is this true? Should a diagnosis of FAS be rendered in an infant who presents with structural evidence of CNS abnormality (microcephaly), but is too young to assess and confirm the presence of CNS dysfunction (intelligence, executive function, memory, language)? Does the presence of the full FAS facial phenotype increase the correlation between microcephaly and brain dysfunction? Who are the birth mothers and birth fathers of these children? What proportion of these patients are still in the care of their birth parents? How satisfied are patients with the services provided by the clinics? Are they provided information/services they were unable to obtain elsewhere? These questions and many more are answered in this report.

METHODS

The Washington State FAS DPN electronic clinical/research database was utilized to construct a comprehensive profile of all 1,400 Washington State residents (birth through adult) who received an interdisciplinary FASD diagnostic evaluation using the FASD 4-Digit Diagnostic Code at one of the seven WA FAS DPN clinics in the first 13 years (1993-2005) of operation. The protocol was approved by the University of Washington Human Subjects Review Board.

Interdisciplinary FASD Diagnostic Model.
All WA FAS DPN clinics use the same interdisciplinary approach[3] to FASD diagnosis using the FASD 4-Digit Diagnostic Code.[6,7]
Interdisciplinary Model. The WA FAS DPN interdisciplinary teams include a pediatrician, two psychologists, a speech-language pathologist, an occupational therapist, a social worker and a family advocate. The patient population served by the WA FAS DPN has expressed strong preference for an evaluation that can be completed in one visit. Thus, a diagnostic evaluation is conducted in one 4-hour session.[3] In preparation for the evaluation, the patient's birth, medical, school, psychological, and social service records are collected by the clinic coordinator and pre-reviewed by the lead psychologist. On the day of the evaluation, the lead psychologist presents the patient's case history, including the outcomes of

any prior medical/psychological assessments, to the team in a 30-minute case conference. While the case-conference is being conducted, the patient's growth is measured and facial photograph is taken for computerized analysis.[10] After the case-conference, the pediatrician and lead psychologist conduct an interview with the caregiver(s) while the child is assessed over a 2-hour period by the second psychologist, speech-language pathologist, and occupational therapist. The child receives a brief physical examination by the pediatrician at the end of their 2-hour assessment. The caregiver interview and child assessment sessions focus on gathering information that is needed for diagnosis and not already present in the child's records. The battery of assessments administered to each patient (both historically and on the day of the diagnostic evaluation) vary by patient age and area of developmental concern. The team reconvenes for 1 hour to derive the FASD 4-Digit Code and generate an intervention plan. The diagnosis and intervention plan are shared with the family in the final 30 minutes of the evaluation. A single comprehensive medical summary documenting the diagnostic outcome, all data used to derive the diagnostic outcome, and intervention recommendations are submitted to the patient's medical record.

The FASD 4-Digit Code. The 4-Digit Code was developed by the UW FAS DPN in 1997 with the most recent 3rd edition published in 2004.[5-8,23] Briefly, the 4 digits of the FASD 4-Digit Code reflect the magnitude of expression of the 4 key diagnostic features of FASD, in the following order: 1. Growth deficiency, 2. FAS facial phenotype, 3. CNS structural/functional abnormalities, and 4. Prenatal alcohol exposure (Figure 1). The magnitude of expression of each feature is ranked independently on a 4-point Likert scale, with 1 reflecting complete absence of the FASD feature and 4 reflecting a strong "classic" presence of the FASD feature. Each Likert rank is specifically case defined. There are 256 possible 4-Digit Diagnostic Codes, ranging from 1111 to 4444. Each 4-Digit Diagnostic Code falls into 1 of 22 unique clinical diagnostic categories (labeled A through V). Seven of the 22 diagnostic categories (4-Digit Categories A–C and E–H) fall broadly under the designation of FASD (A. FAS/Alcohol Exposed, B. FAS/Alcohol Exposure Unknown, C. Partial FAS/Alcohol Exposed, E-F. Static Encephalopathy/Alcohol Exposed, and G-H. Neurobehavioral Disorder/Alcohol Exposed).

FIG. 1A) FASD 4-Digit Diagnostic Code grid. FASD is defined by growth deficiency, specific FAS facial features, evidence of CNS damage/dysfunction, and prenatal alcohol exposure. The 4-Digit Code ranks each of these areas on 4-point, case-defined, Likert scales. The 4-Digit Code (3444) inserted in the grid is 1 of 12 codes that meet the diagnostic criteria for FAS. **B)** FASD 4-Digit Code FAS facial phenotype (**view image**). The Rank 4 FAS facial phenotype determined with the 4-Digit Diagnostic Code requires the presence of all 3 of the following anomalies: (1) palpebral fissure length 2 or more standard deviations below the norm; (2) smooth philtrum (Rank 4 or 5 on the Lip-Philtrum Guide), an (3) thin upper lip (Rank 4 or 5 on the Lip-Philtrum Guide). Examples of the full Rank 4 FAS facial phenotype for Caucasian, Native American, African American, and Asian American children are shown.

FIG. 1A FASD 4-Digit Diagnostic Code Grid

				3	**4**	**4**	**4**		
Severe	Severe	Definite	(4)		X	X	X	(4)	High risk
Moderate	Moderate	Probable	(3)	X				(3)	Some risk
Mild	Mild	Possible	(2)					(2)	Unknown
None	None	Unlikely	(1)					(1)	No Risk
	FAS			Growth	Face	CNS	Alcohol		
Growth Deficiency	**Facial Features**	**CNS Damage**							**Prenatal Alcohol**

Patient Referral Criteria and Diagnostic Capacity

The only criteria required for a patient to be seen in a WA FAS DPN clinic is a confirmed prenatal alcohol exposure history, at any level. The presence of the full FAS facial phenotype (4-Digit Face Rank 4) can be used in lieu of a confirmed alcohol history, since the Rank 4 facial phenotype, as defined by the 4-Digit Code is so specific to prenatal alcohol exposure.[11,12,14] The UW FAS DPN clinic provides evaluations to patients of all ages (newborn to adult). The other statewide FAS DPN clinics focus their services on pediatric populations. The diagnostic capacity of the WA FAS DPN has fluctuated over the years. Current funding levels support 130 evaluations per year: 80 at the UW FAS DPN and 50 at the four statewide FAS DPN clinics.

WA FAS DPN Electronic Clinical/Research Database

All data collected by the WA FAS DPN clinics since 1993 has been entered into an electronic clinical/research database with patient consent and Human Subjects Review Board approval. The majority of the data entered into the database come from two standardized data collection forms: 1) the New Patient Information Form, and 2) the FASD Diagnostic Form. These forms are provided in the Diagnostic Guide for FASD[6] and are posted on the FAS DPN website (**www.fasdpn.org**). The New Patient Information Form is completed by all families requesting an FASD diagnostic evaluation in a WA FAS DPN clinic. The form provides the clinic with key information regarding the patient's sociodemographics, growth, and development, lifetime prenatal and postnatal adverse exposures and events, including prenatal alcohol exposure, and social, educational, medical, psychological, psychiatric, and family history. The FASD Diagnostic Form is designed to capture all information required to derive and support the FASD 4-Digit Diagnostic Code (growth, facial features, CNS structural, neurological, functional measures, prenatal alcohol exposure, all other adverse prenatal and postnatal exposures, events, and conditions including all other physical anomalies and/or syndromes). The FASD Diagnostic Form is completed by the interdisciplinary team at the time of the FASD diagnostic evaluation. Data entered into the FASD Diagnostic Form include all data collected at the time of the FASD diagnostic evaluation as well as all information collected from previous records in preparation for the diagnostic evaluation (birth, medical, school, psychological, psychiatric, social service, placement, and legal records). All data collection forms are reviewed and prepared for data entry into an ACCESS[28] electronic database by SJA. Data is exported from ACCESS to SPSS[29] for statistical analysis. All 4-Digit Codes were upgraded to the most current 2004 version of the FASD 4-Digit Code.[6]

Study Population.

The following inclusion/exclusion criteria were applied to the WA FAS DPN database to establish the study population for this report.

Inclusion Criteria:

1. Received an FASD diagnostic evaluation at one of the seven WA FAS DPN clinics between 1993 and 2005.
2. Was a resident of Washington State at the time of their FASD diagnostic evaluation.
3. Had confirmed prenatal alcohol exposure, at any level. May have an unknown prenatal alcohol exposure history only if their FASD 4-Digit Code diagnostic outcome was full FAS (the Rank 4 FAS facial phenotype is so specific to prenatal alcohol exposure, it can be used in lieu of a prenatal alcohol exposure.[11,12,14,23])
4. Male or female, all ages, all races/ethnicities.

Exclusion Criteria:

1. None.

A total of 1,400 patients met the inclusion/exclusion criteria for this study. Patients evaluated in the WA FAS DPN after 2005 were not included in this study because their data are still in various phases of data entry, monitoring, and cleaning.

Study Groups

The study population was divided into four FASD diagnostic subgroups defined below. A recently completed FASD magnetic resonance study, conducted on a subset of this clinical population, confirmed these first three groups reflect three clinically meaningful and statistically distinct

FASD diagnostic subgroups.[16,23-25] Using the FASD terminology introduced by the Institute of Medicine[30], the SE/AE group most closely reflects 'severe Alcohol-Related Neurodevelopmental Disorder (ARND)' and the ND/AE group most closely reflects 'mild ARND'. The 4th group (Normal CNS/AE) by definition does not fall fully under the umbrella of FASD. This group represents individuals who have a confirmed prenatal alcohol exposure, but present with no evidence of adverse CNS outcomes. Some, but not all, present with growth deficiency and/or FAS facial features. The very existence of this group confirms that not all individual exposed to prenatal alcohol present with evidence of adverse outcomes. Inclusion of this group in this study presents an opportunity to identify potential 'protective' factors against prenatal alcohol exposure. The diagnostic features specific to each group were as follows:

1. *Patients in Group 1* had a 4-Digit diagnosis of **FAS or Partial FAS (FAS/PFAS)** (e.g., 4-Digit Diagnostic Categories A,B,C: with Growth Ranks 1-4, Face Ranks 3-4, CNS Ranks 3 and/or 4, Alcohol Ranks 2-4) (Figure 1). Alcohol Rank 2 (unknown exposure) could only be present if the patient had a diagnosis of full FAS because the Rank 4 FAS facial features are so specific to prenatal alcohol exposure.[11,12,14] In summary, patients in Group 1 had severe cognitive/behavioral dysfunction and the FAS facial phenotype.
2. *Patients in Group 2* had a 4-Digit diagnosis of **Static Encephalopathy / Alcohol Exposed (SE/AE)** (e.g., 4-Digit Diagnostic Categories E,F: with Growth Ranks 1-4, Face Ranks 1-2, CNS Ranks 3 and/or 4, Alcohol Ranks 3-4). In summary, patients in Group 2 had severe cognitive/behavioral dysfunction, comparable to Group 1, but did not have the FAS facial phenotype.
3. *Patients in Group 3* had a 4-Digit diagnosis of **Neurobehavioral Disorder / Alcohol Exposed (ND/AE)** (e.g. 4-Digit Diagnostic Categories G, H: with Growth Ranks 1-4, Face Ranks 1-2, CNS Rank 2, Alcohol Ranks 3-4). In summary, patients in Group 3 had prenatal alcohol exposure comparable to Groups 1 and 2, but in comparison to Groups 1 and 2 had only mild to moderate cognitive/behavioral dysfunction, and did not have the FAS facial phenotype.
4. *Patients in Group 4* had a 4-Digit diagnosis of **Sentinel Physical Findings/Alcohol Exposed** or **No Physical Findings or CNS Abnormalities Detected / Alcohol Exposed (Normal CNS/AE**) (e.g., 4-Digit Diagnostic Categories I and J: with Growth Ranks 1-4, Face Ranks 1-4, CNS Rank 1, and Alcohol Ranks 3-4. In summary, patients in Group 4 had prenatal alcohol exposure, no CNS abnormalities, and may or may not have had growth deficiency and/or FAS facial features.

Data Analysis

Objective 1: Descriptive statistics (means, SDs, proportions) were used to summarize the sociodemographic and clinical profiles of the clinical population as a whole, and each of the four diagnostic subgroups (1. FAS/PFAS; 2. SE/AE; 3. ND/AE; and 4. Normal CNS/AE). Proportions are expressed as valid column percents in all tables unless otherwise specified.

Objective 2: Empirical analyses were conducted to identify risk and protective factors that differentiated the four diagnostic subgroups. Chi-square tests (or Fishers Exact where appropriate) were used to compare proportions between 2 or more subgroups. T-tests were used to compare means between two groups. ANOVA was used to compare means between 3 or more groups. When ANOVA was employed, the overall f-statistic was used to test if differences existed among the group means. When the overall f-statistic was statistically significant, the Duncan post hoc range test was used to identify which group means differed. The Duncan test makes pairwise comparisons using a stepwise procedure. Means are ordered from highest to lowest, and extreme differences are tested first. The Duncan test sets a protection level for the error rate for the collection of tests. The Duncan test identifies homogeneous subsets of means that are not different from one another. For example, if the outcome of a Duncan test is presented as 1,23,4, this means the mean for groups 2 and 3 were comparable to one another, but significantly higher and lower than the means for groups 1 and 4 respectively. Two-tailed p-values of 0.05 were used throughout the analyses. Due to multiple comparisons, resulting p-values should be interpreted accordingly.[31,32] As a

general point of reference (since sample size varied with each analysis), this study had 80% power or greater to detect the following effect sizes (at a two-tailed alpha level of 0.05) when a study group had 65 or more subjects: 1) A difference in means one-half the standard deviation of the mean difference; 2) A 24-point or greater difference in proportions between two groups.

RESULTS

Demand for FASD Diagnostic Services and Ability to Meet the Demand

Although the WA FAS DPN provides FASD diagnostic evaluations to patients from all over the U.S., the vast majority (95%) reside in WA State. Demand for FASD diagnostic services has always exceeded the FAS DPN's capacity, but expansion from the single clinic to a statewide network of clinics doubled its capacity and increased access to FASD diagnostic services. The WA FAS DPN's current capacity is 130 diagnostic evaluations per year. A total of 6,586 families from WA State requested an FASD diagnostic evaluation between 1993 and 2005; on average 506 per year. Patients request an appointment by sending their name and address to the clinic via voicemail or email. All patients requesting an appointment are sent an information packet that includes a description of the clinical services and a New Patient Information Form (NPIF). Patients are requested to complete the NPIF and submit it to the clinic for review. The NPIF documents why a diagnostic evaluation is being requested, what the developmental concerns are, if any, and whether the patient has a confirmed prenatal alcohol exposure. Of the 6,586 requests, 3,004 (47%) completed and submitted the NPIF. In a survey conducted in the mid 1990's, the primary reason stated for not submitting the NPIF was lack of a confirmed prenatal alcohol exposure. Oftentimes, families are requesting evaluations because they are concerned about their child's development, have confirmation of maternal illicit drug use during pregnancy and therefore suspect prenatal alcohol exposure. It has become clear after 17 years of clinical record review that when women use illicit drugs and alcohol during pregnancy, their illicit drug use is far more likely to be documented in medical or social service records than their alcohol use. Of the 3,004 NPIFs submitted, 2,462 (82%) appeared to have a confirmed prenatal alcohol exposure and were thus eligible to be evaluated in clinic. The 18% without a confirmed prenatal alcohol exposure were referred to other appropriate clinics (typically neurodevelopmental clinics). Of the 2,462 patients deemed eligible to be evaluated in the FAS DPN clinics, 1,668 (68%) received a diagnostic evaluation between 1993 and 2005. The average wait to be seen in a clinic, from the time the NPIF was submitted, was 6.7 months. Of the 1,668 patients evaluated in the clinics, 268 were deemed to have an unknown prenatal alcohol exposure, despite what appeared to be a confirmed prenatal alcohol exposure at the time the evaluation was requested. Exclusion of the 268 patients with unknown alcohol exposure produced the sample of 1,400 patients summarized in this report.

FASD Diagnostic Outcomes (Table 1)

Of the 1,400 residents of WA state evaluated in the WA FAS DPN in the first 13 years of operation, 4% were diagnosed with FAS, 7% had PFAS, 28% had Static Encephalopathy (without the FAS facial phenotype), 52% had Neurobehavioral Disorder, 2% presented with growth deficiency and/or FAS facial features, but no evidence of CNS abnormalities, and 7% presented with no growth deficiency, no FAS facial features, and no evidence of CNS structural, neurological, or functional abnormalities, despite their prenatal alcohol exposure. The core clinic at the University of Washington provided diagnostic evaluations for 930 (66%) of the 1,400 patients. The remaining 470 were evaluated at one of the six other FAS DPN statewide clinics. The distribution of FASD diagnoses rendered by the core UW FAS DPN clinic was comparable to the distribution of FASD diagnoses rendered by the six other statewide FAS DPN clinics.

Sociodemographic Profile (Table 2)

Although patients of all races and ethnicities were evaluated in the FAS DPN clinics, the racial distribution of the clinical population was significantly different from the racial distribution of the state ($chi^2 = 100$, $p < 0.000$). The WA State 2000 census reported the following distribution of single races: White 82%, American Indian/Native

Alaskan 2%, Black 3%, Asian 6%).[33] By comparison, Caucasians (48.9%) and Asians (0%) were under-represented in the clinical population and Black (6.6%) and American Indian/Native Alaskan (8.2%) groups were over-represented. Males were significantly more prevalent (58%) than females (42%) (chi^2 18, $p< 0.000$). The vast majority of the population (90%) was under 16 years of age with a mean age of 9.9 years (6.2 SD) and an age range of 7 days old to 50.8 years old. Only 22% percent of the patients were accompanied to clinic by their birth mother. The vast majority (70.5%) were not residing with their birth mother or birth father at the time of their diagnostic evaluation.

Contrasts between FASD Diagnostic Subgroups

Factors A-K below are compared and contrasted between the four clinical subgroups (1. FAS/PFAS, 2. SE/AE, 3. ND/AE, and 4. Normal CNS/AE).

Factors

- **A.** Sociodemographics (Table 2)
- **B.** Birth mother and birth father characteristics (Table 3)
- **C.** Growth (Table 4)
- **D.** FAS facial features (Table 4)
- **E.** CNS structural, neurological, and functional outcomes (Tables 5 and 6)
- **F.** Patient's behavioral profile: Summary of Caregiver Interview and Child Behavior Check List[34] (Tables 7 and 8, Figures 2 and 3)
- **G.** Prenatal alcohol exposure (Table 9)
- **H.** Other prenatal and postnatal risk factors (Table 10)
- **I.** Prevalence of other syndromes (Table 10)
- **J.** Prevalence of mental health disorders (Table 11)
- **K.** Patient satisfaction with the FASD diagnostic process and access to intervention services. (Table 12)

Use of the FASD 4-Digit Code by seven statewide, interdisciplinary teams, over a period of 13 years, produced three clinically and statistically distinct FASD clinical subgroups. The three subgroups (ND/AE, SE/AE and FAS/PFAS) reflected a linear continuum of increasing neuropsychological impairment and physical abnormality, representing the full continuum of FASD.

DISCUSSION

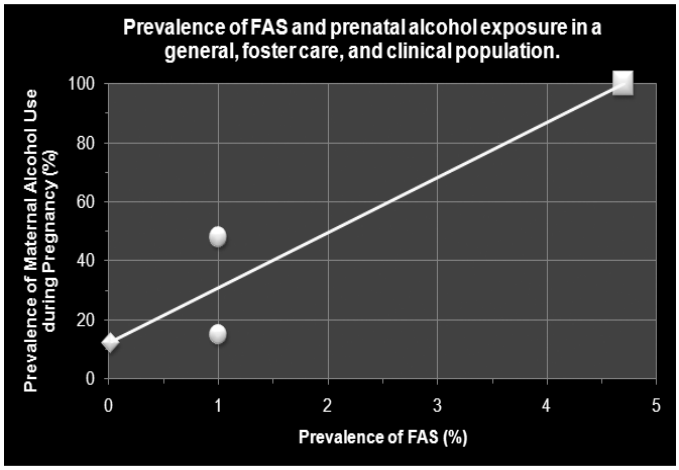
An infinite array of clinical, research, and public health questions can be addressed using the WA FAS DPN clinical dataset. The answers to a selection of questions are presented and discussed below to document the immense value and contribution of a statewide FASD diagnostic program, and underscore the extraordinary value of a comprehensive FASD clinical dataset.

1. Does the prevalence and distribution of the FASD diagnostic outcomes observed in this statewide *clinical* population reflect the prevalence and distribution one would expect to observe in the statewide *general* population?

No. The prevalence of FASD will be higher in this clinical population than in the general population for two reasons: 1) all individuals in this clinical population have a prenatal alcohol exposure, and 2) individuals experiencing difficulties are more likely to be referred to a clinic than those not experiencing difficulties. How much higher will the prevalence be? Below are some FASD prevalence estimates from other population samples (and their corresponding alcohol-exposure estimates) to compare to our clinical sample. The prevalence of FAS in our statewide clinical population was 4.2%. One hundred percent had a confirmed prenatal alcohol exposure. The prevalence of FAS in the King County subset of our statewide clinical population (were Seattle and the University of Washington are located) was 4.7%. Again, 100% had a confirmed prenatal alcohol exposure. In comparison, the prevalence of FAS in a foster care population residing in King County (as documented by a 10-year, active case-ascertainment FAS screening program) was 1.5%.[14] Fifteen percent of this foster care population had a documented prenatal alcohol exposure in their foster records. Forty-eight percent had a confirmed or suspected prenatal alcohol exposure in their foster records. Thus the true prevalence of prenatal alcohol exposure in this foster population was likely somewhere between 15% and 48%. The FAS prevalence estimates from these clinical and high-risk foster populations are 15 to 47 times greater than the FAS prevalence estimate often cited for the general U.S. population (0.1 – 0.3%).[35] National surveys of the general population

estimate 12% of women report drinking during pregnancy.[36] If one plots the prevalence of FAS to the prevalence of alcohol exposure across these three populations (clinical, foster care, and general), an interesting trend appears (Figure 4).

FIG. 4 Prevalence of FAS and prevalence of maternal alcohol use during pregnancy in three populations: ♦General U.S. population (FAS = 0.2%[35], alcohol use = 12.2%[36]). ●King County WA foster care population (FAS = 1%, alcohol use = 15% to 48%).[14] ■King County WA FAS Diagnostic & Prevention Network (FAS DPN) clinical population (FAS = 4.7%, alcohol use = 100%). Best fit linear trend line: y = 18.989x + 12.352; R-squared = 0.89. FAS: fetal alcohol syndrome.



Another related question that is often raised is: How much more prevalent is "ARND" than FAS? The prevalence of SE/AE and ND/AE combined (what other diagnostic systems refer to as ARND[27,30]) was 7.2-fold greater than the prevalence of FAS/PFAS in our clinical population. Does this mean there are 7 times more individuals with ARND than FAS in the *general* population? The true ratio is likely higher for the following reason. Since individuals with severe outcomes are more likely to be referred to a clinic than individuals with less severe outcomes, diagnostic subgroups with the most severe outcomes will likely be disproportionately over-represented in a clinical population. Thus, if FAS is more severe than SE/AE, the prevalence of SE/AE to FAS would likely be higher in the general population than was observed in this clinical population. The published literature suggests ARND is as least three times more prevalent than FAS.[37] Unfortunately, the published literature does not specifically case-define ARND or FAS, so it is difficult to know which of our clinical subgroups to compare them to. The ratio of ARND to FAS, generated from our clinical population, ranges from a low of 2.6-fold (if ARND is defined as SE/AE+ND/AE and FAS is defined as FAS+PFAS) to a high of 18.9-fold (if ARND is defined as SE/AE + ND/AE and FAS is defined as FAS). No matter how one chooses to define ARND and FAS, our clinical data strongly suggest "ARND" is at least 3-fold greater than FAS, but likely much higher. In summary, prevalence estimates derived from clinical populations will exceed those of the general population, but clinical estimates can play an important role in formulating estimates for the general population. An FASD diagnostic clinic is a form of passive population-based FASD screening. The individuals referred are the subset of the general population who were identified by community professionals as at-risk and in need of diagnostic and intervention services.

2. Did the prevalence estimates for FAS/PFAS, SE/AE, and ND/AE vary by race? Yes (Table 13). And these variations were correlated with racial variations in drinking patterns during pregnancy. The prevalence of FAS/PFAS was significantly higher among Caucasians (12.7%) and Blacks (18.5%) than among American/Alaskan Natives (5.2%) (Caucasian versus Native: Chi=5.4, p=0.02; Black versus Native: Chi=9.1, p=0.003). Caucasians and Blacks also reportedly drank significantly more days per week during pregnancy (on average 4.6 and 5.7, respectively) than American/Alaskan Natives (on average 3.6). Interestingly, the only measure of prenatal alcohol exposure that significantly differentiated FAS/PFAS from all other FASD diagnoses, across the entire study population of 1,400, was a higher mean number of days per week of drinking during pregnancy. This same finding was observed in the recently completed FASD magnetic resonance study.[24] Since the window of vulnerability for producing the FAS facial features appears to be very short in duration (a few hours in the mouse[38], a few days in the nonhuman primate[39]), perhaps the more days per week of drinking, the more likely drinking will occur during this narrow window of vulnerability. In contrast to FAS/PFAS, the prevalence of SE/AE "severe ARND without the FAS facial features" was significantly higher in American/Alaskan Natives (41.7%) than in Caucasians (26.6%) or Blacks (20.7%). American/Alaskan Natives reportedly drank a significantly higher number of drinks per drinking occasion during pregnancy than Caucasian or Blacks. Perhaps binge drinking places a fetus at greater risk for CNS structural/functional abnormalities, whereas more frequent drinking increases the odds of also having the FAS facial features.

3. Did the prevalence estimates for FAS/PFAS, SE/AE, and ND/AE vary by age? The prevalence of FAS/PFAS did not vary significantly by age at diagnosis: 0-3.9 yrs (15%), 4-5.9 yrs (9%), 6-10.9 yrs (11%), 11-15.9 yrs (9%), 16+ yrs (10%); Chi=6.3 (p=0.18). An infant was as likely to receive a diagnosis of FAS/PFAS as an adult. As a point of reference, the prevalence of FAS/PFAS across the entire study sample of 1,400 was 11 %. The prevalence of ND/AE varied from 45.3% to 58.4% across the age categories, but these variations were not statistically significant. Again, for reference, the prevalence of ND/AE across all 1,400 subjects was 51.6%. The prevalence of SE/AE did vary significantly by age. Children under the age of 6 years were significantly less likely to receive a diagnosis of SE/AE than older individuals. This may be explained, in part, by the fact that a key clinical feature of SE/AE is significant dysfunction across three or more domains of cognitive/behavioral function. A child typically is not old enough to engage in an assessment of higher level functioning (executive function, memory, language, etc) until they are 7 to 8 years of age. But an individual does not have to have significant dysfunction to meet the CNS criteria for SE/AE. They could meet the criteria with microcephaly. In fact, the CNS criteria for FAS/PFAS and SE/AE are identical (presence of a CNS structural/neurological abnormality and/or significant dysfunction across 3 or more domains of brain function).[6] So why are individuals with SE/AE significantly older (mean = 10.1 years) than individuals with FAS/PFAS (mean = 8.9 years) if the CNS criteria to achieve these two diagnoses are identical? Remember, the only feature that distinguishes FAS/PFAS from SE/AE is the FAS facial phenotype. As it turns out, those with the FAS facial phenotype are significantly more likely to have microcephaly (the prevalence of microcephaly among FAS/PFAS was 45%) than those with comparable brain dysfunction, but no FAS facial phenotype (the prevalence of microcephaly among SE/AE was 25%). This same finding was observed in the recently completed FASD MRI study.[16] More specifically, individuals with FAS/PFAS had significantly and disproportionately smaller frontal lobes than individuals with SE/AE. Since head circumference can be accurately assessed in children less than 8 years of age, but a comprehensive assessment of brain dysfunction cannot, the higher prevalence of microcephaly among the FAS/PFAS group produces a diagnostic subgroup that is significantly younger than the SE/AE subgroup. This observation leads to the next question.

4. Is it clinically cogent to render a diagnosis of FAS in an infant who presents with structural evidence of CNS abnormality (microcephaly), but is too young to assess and confirm the

presence of brain dysfunction (intelligence, executive function, memory, language, etc)? Is the presence of microcephaly in an infant with the FAS facial phenotype predictive of brain dysfunction that will not be revealed until an infant is old enough to participate in higher level functional assessments? The answers to both questions are yes. Among the 154 patients with FAS/PFAS, 69 (44.8%) had microcephaly (Table 5). Of the 69 with microcephaly, 36 (52%) had no evidence of brain dysfunction (Rank 1), 14 (20%) had moderate (Rank 2) brain dysfunction, and 19 (28%) had severe (Rank 3) brain dysfunction. Did the 52% with no evidence of brain dysfunction, truly have normal function, or were they too young to accurately/comprehensively assess function? The data would suggest they were too young to assess. The subset with no evidence of brain dysfunction (Rank 1) had a mean age of 4.7 (6.0 SD) years. The subset with Rank 2 moderate dysfunction had a mean age of 7.5 (5.9 SD) years. And the subset with Rank 3 severe dysfunction had a mean age of 10.3 (5.9 SD) years. The older the patient, the more likely they revealed evidence of moderate to severe dysfunction (ANOVA F=5.8 (df 2), p=.005). This data suggests rendering a diagnosis of FAS/PFAS in a newborn/infant that presents with microcephaly, but is too young to assess/confirm brain dysfunction, is clinically sound. The combined presence of the FAS facial phenotype, microcephaly, and prenatal alcohol exposure serves as a strong risk factor for (predictor of) brain dysfunction. The correlations between increasing magnitude of expression of the 4-Digit FAS facial phenotype and 1) increasing CNS dysfunction ,and 2) decreasing head circumference are quite high (Figures 5A,B).[11,16] Early diagnosis affords early intervention. Postponing a FAS/PFAS diagnosis in children with microcephaly, who were not old enough to participate in higher-level functional assessments to confirm brain dysfunction, could lead to missed opportunities for early intervention.

FIG. 5A) The mean Performance Intelligence Quotient (PIQ) standard score (WISC III [40]) decreased significantly as the FAS facial phenotype increased in magnitude from 4-Digit Face Rank 1 to 4 (ANOVA: F 2.7(3df), p =.046).

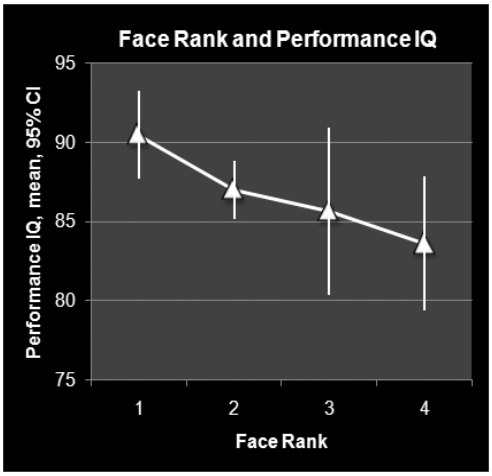
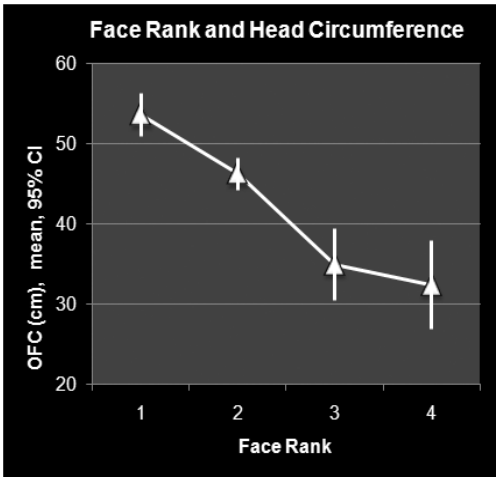


FIG. 5B) The mean occipital frontal head circumference (OFC) in centimeters (cm) decreased significantly as the FAS facial phenotype increased in magnitude from 4-Digit Face Rank 1 to 4 (ANOVA: F 26 (3df), p < .001).



5. Do the CNS functional profiles of the FAS/PFAS, SE/AE and ND/AE groups differ when generated by a single, age-appropriate, comprehensive neuropsychological battery administered to all patients, as compared to when generated by variable neuropsychological batteries that may focus more on deficits than strengths (as is often the case in clinical settings)? The CNS functional profiles of the FAS/PFAS, SE/AE, and ND/AE groups presented in Table 6 were generated from two primary sources of data: 1) past school/psychological assessments, and 2) current assessments conducted at the time of the FASD diagnostic evaluation. These school and clinic-based assessment protocols are more likely to target areas of deficit (rather than areas of strength) because the primary goals of these assessments are to determine if an individual qualifies for school-based services or meets established FASD diagnostic criteria. As a result, no two patients in the FAS DPN clinical dataset necessarily received the same test battery, and their test batteries likely focused more on their deficits than their strengths. This could lead to group profiles that under estimate the mean performance levels of each group as a whole. If every patient received the same age-appropriate test battery, and the battery assessed all areas of function, not just the areas with perceived deficits, how different might the profiles be? The recently completed FASD magnetic resonance research study provided an opportunity to answer this question.[24] Sixty-five children across the full continuum of FASD were randomly selected for enrollment into the magnetic resonance study from among these 1,400 WA FAS DPN patients. As a standard of research protocol, a single, comprehensive neuropsychological battery was administered to all 65 children.[24] The CNS functional profiles generated by the single, comprehensive research battery[24] were near identical to the functional profiles generated by the more variable, less comprehensive clinical batteries (Table 6). For example, the mean FSIQ[40] standard scores for the FAS/PFAS, SE/AE, and ND/AE groups in the magnetic resonance study were 77.5, 79.3, and 99.2 respectively. The mean Visual Motor Integration[41] total standard scores for the FAS/PFAS, SE/AE, and ND/AE groups in the magnetic resonance study were 76.2, 81.4, and 90.9 respectively. The mean Rey Complex Figure Test[42] Copy Raw Scores for the FAS/PFAS, SE/AE, and ND/AE groups in the magnetic resonance study were 17.4, 20.5, and 25.6 respectively. These outcomes suggest the CNS profiles presented in Table 6 were not markedly influenced by the variable clinical batteries used to generate them.

6. Do FASD diagnostic outcomes vary by level of prenatal alcohol exposure? Yes (Table 9). Individuals with FAS/PFAS had a significantly higher mean number of days per week (5.6) of prenatal alcohol exposure than individuals with a comparable level of CNS dysfunction, but no facial features (SE/AE) (4.3 days/week) ,or individuals with less severe CNS dysfunction and no facial features (ND/AE) (4.4 days/week). This same finding was observed in the FASD magnetic resonance study.[24]

7. Is the presence of other adverse exposures/events (e.g., prenatal exposure to illicit drugs, poor prenatal care, multiple home placements, physical/sexual abuse) associated with more severe developmental outcomes? Yes (Table 10). Prenatal alcohol exposure was rarely, if ever, the sole risk factor present among patients evaluated at the WA FAS DPN. One third of the population had no documented prenatal care. Ninety-three percent had other adverse prenatal exposures (e.g., tobacco, illicit drugs). Seventy percent were no longer in the care of their birth parents and had on average three out-of-home placements. At least 34% were physically abused and 24% sexually abused. Seventy-five percent had one or more mental health disorders documented in their medical record. The prevalence of adverse exposures and events was for the most part, comparably high across the three FASD groups (e.g., tobacco, illicit drug use, neglect, out-of-home placements). Occasionally the prevalence increased incrementally with increasing severity of FASD diagnostic outcome from NE/AE to SD/AE to FAS/PFAS (e.g., no prenatal care). Most striking, however, were the contrasts observed between the three FASD groups and Group 4 (the group with no evidence of CNS abnormality). Physical and sexual abuse was 2- to 5-fold more prevalent in the FASD groups than in Group 4. Children in the FASD

groups were twice as likely to be in adoptive care and significantly less likely to receive prenatal care than children in Group 4. Prenatal exposure to alcohol and other illicit drugs was comparably high across all four groups.

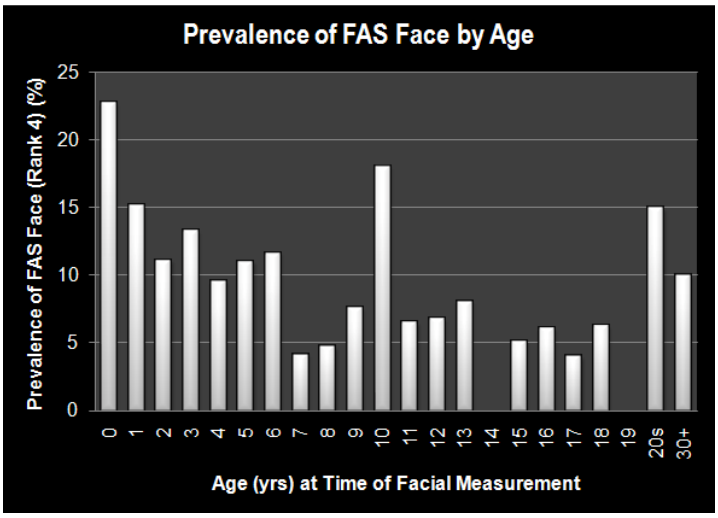
8. What proportion of individuals with prenatal alcohol exposure present with no evidence of CNS structural, neurological, or functional abnormalities? Were they exposed to less alcohol? Of the 1,400 subjects with prenatal alcohol exposure, 130 (9.3%) presented with no evidence of CNS abnormality (Table 1). Ninety-six of the 130 subjects in Group 4 presented with no growth or FAS facial features either. Although one might expect to see a lower reported alcohol exposure among this group, their reported level of exposure was comparable to that of the SE/AE and ND/AE groups. Three features that did distinguish this unaffected group from the other groups were their gender, age, and postnatal adverse experiences. The unaffected group was significantly more likely to be female (57.7%) than the other FASD clinical subgroup (FAS/PFAS 48.1%; ND/AE 41.6%; SE/AE 35.3%). And the unaffected group was significantly younger (46.2% were under 4 years of age) compared to 25.3% among the FAS/PFAS, 10.7% among the SE/AE, and 16.2% among the ND/AE. It is likely that some of the subjects in the unaffected group were classified as functionally within the normal range because they were too young to assess and rule-out higher level functional deficits. The only way an infant could meet the CNS functional criteria for SE/AE is with significantly delayed mental and motor development (e.g., Mental and Motor Developmental Index standard scores of 50 on the Bayley Scales of Infant Development[43]). But young age does not explain why the 130 patients in Group 4 did not meet the CNS functional criteria for ND/AE. A third factor that markedly differentiated the unaffected group from the three affected groups was adverse postnatal experiences. As reported above, the unaffected group was significantly less likely to experience high-risk (Rank 4) postnatal adverse events like physical or sexual abuse.

9. How often are other syndromes present in this patient population? Eighteen (1.3%) of the 1,400 subjects were diagnosed with other syndromes (Table 10). Only one of the seven clinics had a dysmorphologist on their interdisciplinary team. When the prevalence estimate was restricted to the 664 patients seen at the UW FAS DPN between 1993 and 1999 when a dysmorphologist served as the pediatrician on the team, 13 (1.9%) were identified with other syndromes. When syndromes other than FAS were suspected by the other pediatricians on the teams (the pediatricians who were not dysmorphologists or geneticists), the patients were referred to a geneticist. Of the 736 patients seen by the other pediatricians 5 (0.7%) were documented to have another syndrome and an additional 8 (1.1%) were suspected to have another syndrome and were referred to a geneticist. Thus, the pediatricians documented or suspected the same proportion of patients with other syndromes (1.8%) as was diagnosed when a dysmorphologist was on the team (1.9%). It is worth noting that one child diagnosed with FAS in the WA FAS DPN also had Down syndrome. Alcohol is a teratogen to all developing fetuses, including those with genetic disorders. The child presented with growth deficiency below the 2nd percentile on a growth chart for children with Down syndrome. The child presented with the facial features of Down syndrome and FAS. The facial features of Down syndrome are distinct from the facial features of FAS. The two phenotypes were readily apparent and easily distinguished. The child presented with microcephaly (3 SDs below the mean for boys with normal development, 1 SD below the mean for children with Down syndrome). The child presented with Bayley[43] Motor and Mental Index scores below 50; a level of developmental delay that can be observed in both Down syndrome and FAS. The birth mother was reported to have consumed alcohol daily throughout pregnancy.

10. The FASD literature suggests that infants and adults are less likely to present with the full FAS facial phenotype than school-aged children. Is there evidence of this in this dataset? No. The proportion of subjects who presented with the full FAS facial phenotype (Rank 4) by age group was as follows: birth to 3.9 yrs (36/258, 14%), 4 to 16.9 years (78/1001, 7.7%), and 17 to 53 years (12/141, 9.5%). The age group with the highest prevalence of the FAS facial phenotype was infants under one year of age (23%) (Figure 6).

Profile of the first 1,400 patients receiving diagnostic evaluations for fetal alcohol spectrum disorder at the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network

FIG. 6 Proportion of patients in each age group who presented with the full Rank 4 FAS facial phenotype at the time (age) of their FASD diagnostic evaluation.



11. Growth deficiency has always been a hallmark of FAS/D. How prevalent is growth deficiency in this patient population? Only 34.1% of the 1,400 subjects presented with height and/or weight below the 10th percentile (Growth Ranks 2, 3 or 4). Only 7.9% presented with height and weight below the 3rd percentile (Growth Rank 4). Of the patients with FAS/PFAS, 35.7% presented with no growth deficiency (Growth Rank 1: height nd weight above the 10th percentile) and thus received a diagnosis of PFAS.

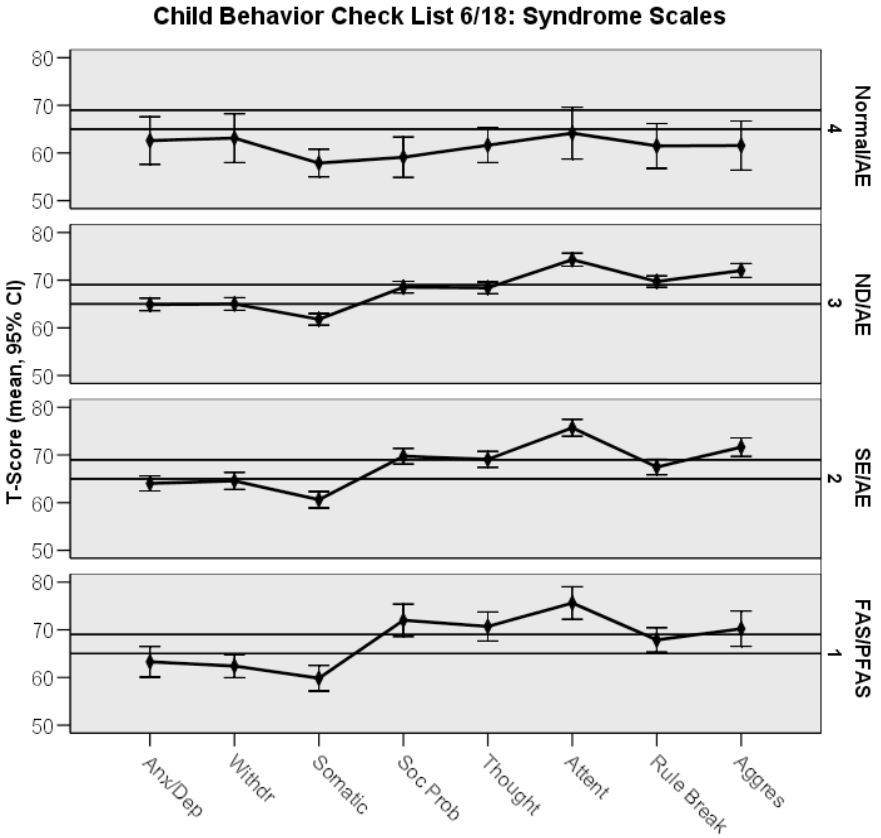
12. Who are the birth fathers of these children? The names of 76% of the birth fathers were known, compared to 95% of the birth mothers. The more severe the FASD diagnostic outcome, the less likely the birth father's name was documented in the child's records. Only 7.6% of them accompanied their child to the FASD diagnostic evaluation. The fathers were on average 29 years old at the birth of their child with FASD and 38 years old at the time the child was being diagnosed with FASD (Table 3). Thirty-nine percent did not finish high school, 45% completed high school, and 16% attended college. They were in general, older and more highly educated than the birth mothers. Approximately half of them reportedly had learning disabilities.

13. What proportion of patients were no longer in the care of their birth parents at the time of their FASD diagnostic evaluation? Seventy percent of the patients were no longer in the care of either birth parent at the time of their FASD diagnostic evaluation (Table 1). The average number of home placements across the 1,400 patients was 2.9 $\pm$ 3.1. Nineteen percent had four or more home placements.

14. Does a caregiver's impression of their child's behavior differ between FAS/PFAS, SE/AE, and ND/AE? Yes and No. Among the 1,270 caregivers who completed the Child Behavior Checklist[34] (for children 6 to 18 years of age), the prevalence and magnitude of behavior problems was comparably high across all FASD subgroups. Attention problems were reported most often (Table 7, Figure 2). When the results of the 2-hour, structured interview with the caregiver(s) (conducted by the medical doctor and psychologist on the day of the FASD diagnostic evaluation) were tabulated (Table 8, Figure 3), the

prevalence and magnitude of behavioral concerns often increased significantly and incrementally as one advanced from the ND/AE to SE/AE to FAS/PFAS group. It is important to note that these parent impressions of their child's behavior were recorded before the parent or the clinicians knew the FASD diagnostic outcome of the child.

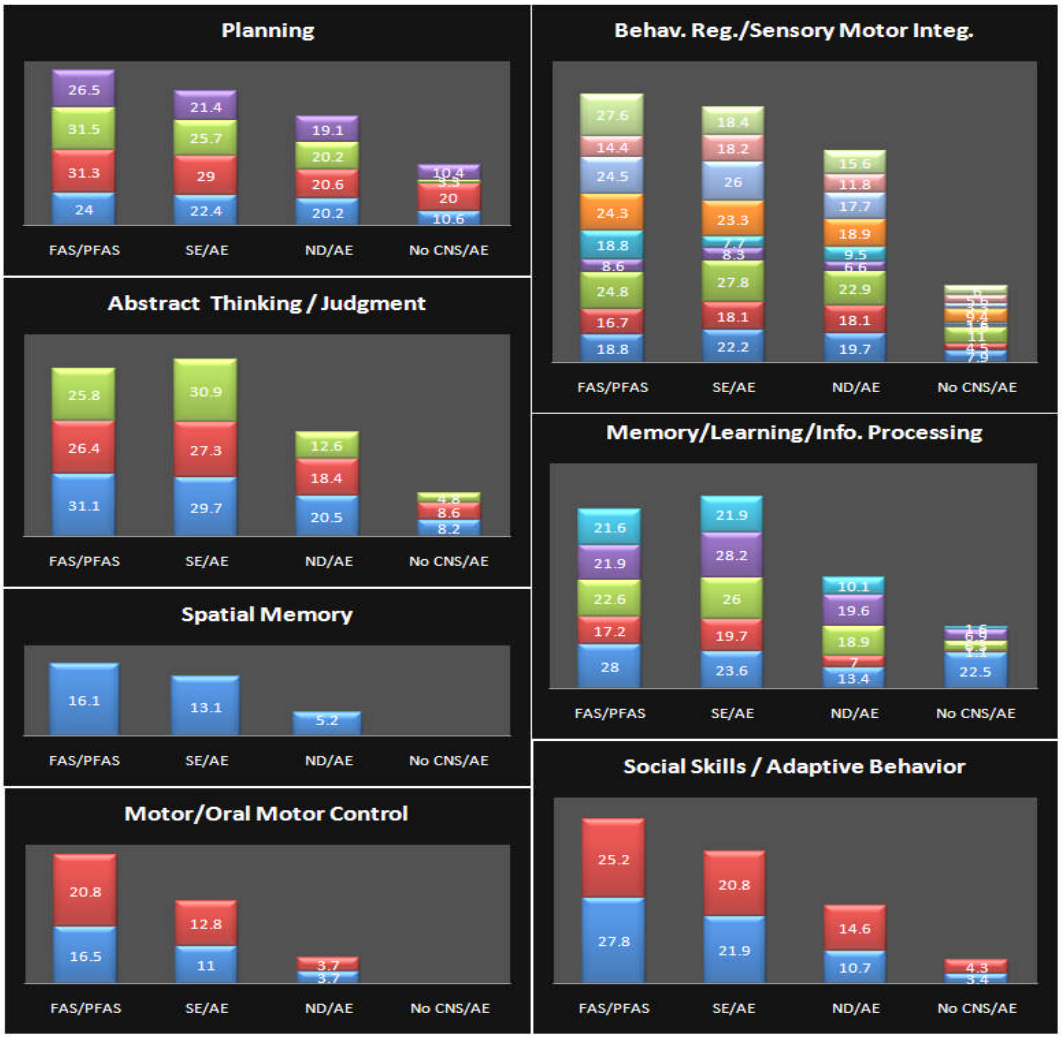
FIG. 2 Child Behavior Check List[34] (CBCL/ 6-18) Syndrome Scales (*see* Table 7) among the 516 patients administered a CBCL when they were between 6 and 18 years of age. All abbreviations are defined in Table 7.



Profile of the first 1,400 patients receiving diagnostic evaluations for fetal alcohol spectrum disorder at the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network

FIG. 3 Proportion of patients classified by the pediatrician as 'significantly delayed/impaired' in behaviors addressed in a 2-hour, structured caregiver interview administered jointly by the pediatrician and psychologist during the FASD diagnostic evaluation. This is a graphical presentation of the data presented in Table 8 to illustrate the cumulative increase in impairment as one advances across the study groups. Each color in a bar reflects the behaviors listed in Table 8 under each Domain. Abbreviations are defined in Table 8. The number printed in each colored section is the proportion of patients with significant impairment for that behavior. For example, the bar for the FAS/PFAS group in the Planning Domain reflects the following: blue square (24% present with significant impairment for "Needs considerable help organizing daily tasks"); red square (31.3% present with significant impairment for "Cannot organize time"); green square: (31.5% present with significant impairment for "Does not understand concept of time"); and purple square (26.5% present with significant impairment for "Difficulty carrying out multistep tasks").

.



15. What is the prevalence of other mental health disorders in this patient population? Among the 1,064 patients, five or more years of age at the time of their FASD diagnostic evaluation, 82% had one or more mental health disorders documented in their medical records (Table 11). The most prevalent was ADD/ADHD (53.9%). Despite this high overall prevalence, the prevalence estimates for each disorder (based on review of medical records available to the FASD clinics) may substantially under-estimate the true prevalence of each disorder. Many of these disorders fail to be formally diagnosed and recorded in the medical record. When a representative subset of these children (n=65) were administered the Computerized Diagnostic Interview Schedule for Children[44] during their enrollment in the FASD magnetic resonance study[24], the prevalence estimates for many disorders were substantially higher. For example, Oppositional Defiant Disorder was reported in 6.8% of this clinical population, but was diagnosed in 52% of the subset that participated in the magnetic resonance study. Obsessive compulsive disorder was reported in 0.7% of this clinical population, but was diagnosed in 9.2% of the subset that participated in the magnetic resonance study.

16. Were patients satisfied with the interdisciplinary FASD diagnostic evaluation process? Were they provided information they were unable to obtain elsewhere? Was the 4-Digit Code approach to diagnosis easy to understand? Was their ability to access and benefit from recommended intervention services influenced by what diagnosis their child received under the umbrella of FASD? Would they recommend the clinic to other families with similar needs? A 10-question patient satisfaction survey has been sent to all patients evaluated at the UW FAS DPN clinic since 1993. The survey may be completed anonymously and comes with a stamped-addressed return envelope to maximize participation in the survey. Patients universally expressed high satisfaction for the FASD diagnostic services provided by the University of Washington (Table 12). Ninety-nine percent would recommend the Clinic to other families with similar needs. Ninety-one percent said they received information they were unable to obtain elsewhere, despite the fact the clinic is located in a large metropolitan area (Seattle) with many genetic, neurodevelopmental, and psychological evaluation services available. Eighty-six percent found the explanation of the diagnosis using the 4-Digit Code easy to understand. And perhaps most informative; family's whose child received a diagnosis of SE/AE or ND/AE were as likely to report successfully accessing and benefiting from recommended intervention services as family's whose child received a diagnosis of FAS/PFAS. This is in contrast to the oft stated belief that a family will not qualify for services if the diagnosis is not FAS/PFAS or at least given a name that implies alcohol is the causal agent (e.g., ARND). Overall, 82.1% of families reported being somewhat to very successful in finding the recommended intervention services and 83.7% reported these services met some to all of their needs.

Strengths and Limitations

The outcomes presented in this report reflect a very large, 13-year, statewide, clinical population of patients (newborn to adult) who all received an identical, interdisciplinary approach to FASD diagnostic evaluation using the FASD 4-Digit Code. By virtue of this, the outcomes presented in this report are highly representative of the study's intended target population (a statewide clinical population of individuals with prenatal alcohol exposure seeking an FASD diagnostic evaluation). The outcomes presented in this report should not be construed to represent the population of *all* individuals exposed to prenatal alcohol exposure. Even though the only requirement to obtain an FASD diagnostic evaluation in the WA FAS DPN is a confirmed prenatal alcohol exposure, alcohol-exposed individuals with developmental concerns are more likely to be referred to the clinic than alcohol-exposed individuals with no developmental concerns. Other features inherent to this clinical dataset should also be taken into consideration when interpreting the reported outcomes. 1) Data in the FAS DPN clinical dataset are obtained from a variety of sources (medical/educational/social service record review,

caregiver interview, and direct clinical evaluation). The accuracy of the data will vary by source. 2) No two patients have an identical dataset. The amount and type of data available on each patient varies by their age and the existence and availability of previous medical/educational assessments. 3) Prior medical and educational assessments may focus more on areas of concern than areas of strength. As a result, inclusion of these data sources could generate group profiles that over represent deficits. Overall, clinical datasets are an invaluable, ubiquitous resource that, when interpreted in the proper context can greatly inform and advance a field.

CONCLUSION

In summary, the existence of the WA FAS DPN diagnostic program and electronic database over the past 17 years confirms it is possible to establish and maintain a comprehensive statewide FASD diagnostic program and dataset. As demonstrated in this report, a broad array of clinical, research, and public health questions can be addressed with a FASD clinical dataset. The outcomes presented in this report reflect the experience of WA State. With the worldwide replication of this interdisciplinary approach to FASD diagnosis using the 4-Digit Code, the opportunity now exists, for the first time ever, to construct and validly compare clinical profiles across very diverse, geographically dispersed populations. This report serves as a formal appeal to FASD clinical programs worldwide to do just that. The benefits to individuals with FASD and their families would be immense.

Acknowledgements

The WA FAS DPN has been supported over the past two decades by the following organizations: Centers for Disease Control and Prevention (1992-1997, U84/CCU008707); Western Washington Chapter of the National March of Dimes Birth Defects Foundation (1995); Washington State Department of Social and Health Services, Division of Alcohol and Substance Abuse through the passage of Senate Bill SB5688 (1997-present, 0965- 69095); and the Chavez Memorial Fund (2002-present). Support has also received from the Center on Human Development and Disability, University of Washington since 1993 (National Institute of Child Health and Human Development grant P30 HD02274). The creation of this clinical dataset would not have been possible without the extensive clinical efforts and support of the interdisciplinary diagnostic teams and community health/social service agencies in Seattle, Everett, Federal Way, Tacoma, Yakima, Spokane, and Pullman. And finally, special thanks are extended to the patients and their families for their benevolent contributions to the WA FAS DPN dataset.

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TABLE 1 FASD 4-Digit Diagnostic Categories within each of the four FASD diagnostic study subgroups.

Characteristic	FASD Diagnostic Subgroups										Statistics
	1. FAS/PFAS		2. SE/AE		3. ND/AE		4. Normal CNS/AE		Total		Chi-square Chi (p)
	N = 154		N = 394		N = 722		N = 130		N = 1400		
4-Digit Code FASD Diagnostic Categories (A-C, E-J): N (valid %)											
A. FAS / Alcohol Exposed	52	33.8							52	3.7	
B. FAS / Alcohol Exposure Unknown	7	4.5							7	0.5	
C. Partial FAS / Alcohol Exposed	95	61.7							95	6.8	
E. Sentinel Physical Findings / Static Encephalopathy / Alcohol Exposed			95	24.1					95	6.8	
F. Static Encephalopathy / Alcohol Exposed			299	75.9					299	21.4	
G. Sentinel Physical findings / Neurobehavioral Disorder / Alcohol Exposed					160	22.2			160	11.4	
H. Neurobehavioral Disorder / Alcohol Exposed					562	77.8			562	40.1	
I. Sentinel Physical Findings / Alcohol Exposed							34	26.2	34	2.4	
J. No Sentinel physical findings or CNS abnormalities detected / Alcohol Exposed							96	73.8	96	6.9	
Diagnostic outcomes across FAS DPN clinics: N (valid row %)											3.2 (.36)
University of Washington Core Clinic in Seattle	107	11.5	248	26.7	487	52.4	88	9.5	930	100	
Six other statewide FAS DPN clinics	47	10.0	146	31.1	235	50.0	42	8.9	470	100	

Abbreviations: Chi: chi-square test statistic across the four study groups. FAS: fetal alcohol syndrome. P: p-value. PFAS: partial FAS. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. SE/AE: Static encephalopathy/alcohol exposed.

Profile of the first 1,400 patients receiving diagnostic evaluations for fetal alcohol spectrum disorder at the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network

TABLE 2 Sociodemographic profiles across the four study groups.

Characteristic	FASD Diagnostic Subgroups										Statistics		
	1. 59 FAS/ 95 PFAS		2. SE/AE		3. ND/AE		4. Normal CNS/AE		Total		ANOVA Overall	ANOVA Post Hoc	Chi-square
	N = 154		N = 394		N = 722		N = 130		N = 1400		F (p)[A]	Duncan[B]	Chi (p)
Gender: N (valid%)													
male	80	51.9	255	64.7	422	58.4	55	42.3	812	58.0			22.8(.00)
Race (one race): N (valid%)													
White	87	56.5	182	46.2	357	49.4	58	44.8	684	48.9			30.2(.00)
Black	17	11.1	19	4.8	45	6.2	11	8.5	92	6.6			
American Indian/Native Alaskan	6	3.9	48	12.2	57	7.9	4	3.1	115	8.2			
Asian	0	0	0	0	0	0	0	0	0	0			
All others (including mixed race)	44	28.6	145	36.8	263	36.4	57	43.8	509	36.4			
Age at diagnosis (yr): N(row-column valid%)													
0 – 3.9	39	15.1-25.3	42	16.3-10.7	117	45.3-16.2	60	23.3-46.2	258	100-18.4			116(.00)
4 – 5.9	22	9.4-14.3	52	22.3-13.2	136	58.4-18.8	23	9.9-17.7	233	100-16.6			
6 – 10.9	53	11.0-34.4	157	32.6-39.8	251	52.1-34.8	21	4.4-16.2	482	100-34.4			
11 – 15.9	26	9.1-16.9	93	32.5-23.6	149	52.1-20.6	18	6.3-13.8	286	100-20.4			
16+	14	9.9-9.1	50	35.5-12.7	69	48.9-9.5	8	5.6-6.2	141	100-10.1			
Mean (SD)	8.9	8.3	10.1	6.1	8.9	5.5	6.7	7.0	9.0	6.2	10.2(.00)	3,12,4	
Minimum-Maximum	0.3	50.5	0.5	50.8	0.5	36.6	.02	48.1	0.02	50.8			
Patient's caregiver at diagnosis: N (valid%)													
Birth mother	26	17.3	79	21.4	152	21.9	36	28.6	293	21.9			[C] 6.5(.09)
Birth Father	10	6.7	34	9.2	47	6.8	11	8.7	102	7.6			
Other biological family member	25	16.7	39	10.6	123	17.7	25	19.8	212	15.8			
Adoptive parent	39	26.0	81	22.0	155	22.3	15	11.9	290	21.6			
Foster parent	35	23.3	80	21.7	149	21.4	29	23.0	293	21.9			
Social or caseworker	5	3.4	16	4.3	17	2.5	2	1.6	40	3.0			
Other	10	6.7	40	10.8	52	7.5	8	6.3	110	8.2			
Annual income < $35,000: N (valid%)	37	59.7	98	66.2	210	64.6	40	67.8	385	64.8			0.9(.82)

Abbreviations: Chi: chi-square test statistic across the four study groups, unless otherwise noted. F: F statistic. FAS: fetal alcohol syndrome. P: p-value. PFAS: partial FAS. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. SD: standard deviation. SE/AE: Static encephalopathy/alcohol exposed. Notations: A. Numerator degrees of freedom = 3; denominator df = total sample size minus 4. B. The Duncan multiple comparisons range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at $p < 0.05$. C. Birth parent versus not birth parent.

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TABLE 3 Birth mother and birth father characteristics across the four study groups.

Characteristic	FASD Diagnostic Subgroups										Statistics		
	1. 59 FAS/ 95 PFAS		2. SE/AE		3. ND/AE		4. Normal CNS/AE		Total		ANOVA		Chi-square
											Overall	Post Hoc	
	N = 154		N = 394		N = 722		N = 130		N = 1400		F (p)[A]	Duncan[B]	Chi (p)
MOTHER													
Mother's name known	143	93.3	370	93.9	683	94.6	129	99.2	1325	94.6			6.8(.08)
Mother attended FASD evaluation: N (valid%)	26	17.3	79	21.4	152	21.9	36	28.6	293	21.9			5.2(.16)
Mother's age (yr)													
At child's birth: N mean (SD)	119	28.3 (6.6)	318	25.5 (6.1)	594	25.6 (6.3)	116	25.8 (5.9)	1147	25.9 (6.3)	6.6(.00)	1,234	
Min-Max	16.0	43.0	15.0	41.0	14.0	43.0	14.2	42.0	14.0	43.0			
At FASD diagnosis: N mean (SD)	119	37.1 (10.6)	318	35.4 (8.5)	594	34.5 (8.2)	116	32.4 (9.1)	1147	34.8 (8.7)	6.6(.00)	1,234	
Min-Max	22.1	81.5	19.3	77.6	17.5	75.3	16.0	79.1	16.0	81.5			
Maternal highest education level: N (valid%)													1.8(.61)
Did not finish high school	56	53.3	166	57.6	272	52.8	59	55.1	553	54.5			
Finished high school	37	35.2	91	31.6	171	33.2	26	24.3	325	32.0			
College	12	11.5	31	10.8	72	14.0	22	20.6	137	15.6			
Maternal learning disabilities: N (valid%)	57	56.4	168	60.6	291	59.5	47	50.0	563	58.6			6.4(.38)
Mother deceased: N (valid%)	9	12.3	17	8.8	34	9.6	2	2.6	62	8.9			5.1(.17)
Parity of index child: N mean (SD)	122	3.0 (1.8)	317	2.7 (1.8)	600	2.7 (1.7)	117	2.7 (1.7)	1156	2.7 (1.7)	1.0(.39)	--	
Min-Max	1	9	1	12	1	10	1	9	1	12			
Gravity of index child: N mean (SD)	83	3.5 (2.2)	174	3.1 (2.2)	322	3.2 (2.0)	52	2.9 (1.6)	631	3.2 (2.0)	1.2(.30)	--	
Min-Max	1	9	1	12	1	11	1	9	1	12			
FATHER													
Father's name known	105	68.2	299	75.9	555	76.9	107	82.3	1066	76.1			8.3(.04)
Father attended FASD evaluation: N (valid%)	10	6.7	34	9.2	47	6.8	11	8.7	102	7.6			2.4(.49)
Father's age (yr)													
At child's birth: N mean (SD)	62	31.5 (8.4)	189	29.4 (7.3)	369	28.7 (7.3)	70	27.8 (7.4)	690	29.0 (7.5)	3.5(.02)	1,234	
Min-Max	17	66	15	61	15	62	14	48	14	66			
At FASD diagnosis: N mean (SD)	62	40.6 (13.2)	189	39.6 (9.2)	369	38.1 (9.8)	70	35.1 (10.3)	690	38.4 (10.1)	4.5(.00)	123,4	
Min-Max	19	87	23	81	20	87	15	65	15	87			
Paternal highest education level: N (valid%)													
Did not finish high school	21	33.9	79	40.9	129	38.4	22	36.7	248	38.5			[C] 1.5(.68)
Finished high school	32	51.6	85	45.7	153	45.5	22	36.7	292	45.3			
College	9	14.5	25	13.4	54	16.1	16	26.6	104	16.2			
Paternal learning disabilities: N (valid%)	22	43.1	97	53.9	165	54.3	24	38.7	308	51.6			6.9(.33)

Abbreviations: Chi: chi-square test statistic across the four study groups, unless otherwise noted. F: F statistic. FAS: fetal alcohol syndrome. P: p-value. PFAS: partial FAS. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. SD: standard deviation. SE/AE: Static encephalopathy/alcohol exposed. Notations: A. Numerator degrees of freedom = 3; denominator df = total sample size minus 4. B. The Duncan multiple comparisons range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at $p < 0.05$. C. Did versus did not finish high school.

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TABLE 4 Growth and FAS facial outcomes across the four study groups.

Characteristic	FASD Diagnostic Subgroups										Statistics		
	1. 59 FAS/ 95 PFAS		2. SE/AE		3. ND/AE		4. Normal CNS/AE		Total		ANOVA Overall	ANOVA Post Hoc	Chi-square
	N = 154		N = 394		N = 722		N = 130		N = 1400		F (p)[A]	Duncan[B]	Chi (p)
GROWTH													
Growth Rank in 4-Digit Code: N (%)													
Rank 1	[C] 55	35.7	245	62.2	532	73.7	91	70.0	923	65.9			165(.00)
Rank 2	21	13.6	54	13.7	109	15.1	18	13.8	202	14.4			
Rank 3	35	13.6	52	13.2	58	8.0	19	14.6	164	11.7			
Rank 4	43	27.9	43	10.9	23	3.2	2	1.5	111	7.9			
Gestational age (wks): N mean (SD)	116	36.8 (3.2)	286	37.1 (3.5)	529	37.7 (3.0)	86	37.7 (2.7)	1017	37.4 (3.2)	4.2(.00)	12,234	
Birth weight percentile: N mean (SD)	124	33.2 (28.9)	284	48.0(32.6)	532	52.0(30.2)	93	45.7 (28.7)	1033	48.1 (31.1)	13.0(.00)	1,234	
Birth length percentile: N mean SD)	103	36.5 (34.7)	222	52.7 (34.5)	440	56.9 (31.9)	79	52.5 (30.9)	844	52.9 (33.4)	10.6(.00)	1,234	
Wgt percentile at diagnosis: N mean (SD)	143	33.6 (32.4)	367	47.6 (32.8)	661	53.9 (29.9)	119	53.3 (29.0)	1290	49.8 (31.6)	17.9(.00)	1,234	
Hgt percentile at diagnosis: N mean (SD)	143	25.1 (26.9)	364	38.3 (31.6)	664	42.6 (29.6)	119	39.5 (29.2)	1290	39.1 (30.3)	13.7(.00)	1,234	
FACE													
Face Rank in 4-Digit Code: N (%)													
Rank 1	0	0	93	23.6	210	29.1	55	42.3	358	25.6			816(.00)
Rank 2	0	0	301	76.4	413	57.2	58	44.6	772	55.1			
Rank 3	[D] 69	44.8	0	0	65	9.0	10	7.7	144	10.3			
Rank 4	85	55.2	0	0	[E] 34	4.7	[F] 7	5.4	126	9.0			
Mean PFL zscore: mean (SD)	-3.2	1.2	-2.6	1.6	-2.3	1.4	-1.9	1.5	-2.4	1.5	24(.00)	1,2,3,4	
Mean PFL $\leq$ -2 SD: N (valid%)	144	93.5	260	66.0	418	57.9	59	45.4	881	62.9			90(.00)
Innercanthal distance zscore: mean (SD)	-0.1	1.1	0.1	1.7	0.2	1.2	0.2	1.0	0.1	1.4	1.4(.24)		
Innercanthal distance $\geq$ 2SD: N (valid%)	4	5.3	20	9.3	19	5.7	4	8.5	47	7.0			3.2(.36)
Philtrum Smoothness Rank: N (valid%)													
1 (very deep)	0	0	99	25.4	178	24.9	57	44.2	334	24.2			408(.00)
2 (somewhat deep)	0	0	134	34.4	218	30.5	27	20.9	380	27.5			
3 (normal)	[G] 30	20.0	111	28.5	200	28.0	24	18.6	365	26.4			
4 (almost smooth)	76	50.7	34	8.7	101	14.1	14	10.9	225	16.3			
5 (completely smooth)	44	29.3	11	2.8	17	2.4	7	5.4	79	5.7			
Upper Lip Thinness Rank: N (valid%)													
1 (very thick)	0	0	121	31.1	180	25.2	36	27.9	337	24.1			248(.00)
2 (moderately thick)	0	0	105	27.0	178	24.9	34	26.4	317	22.6			
3 (normal)	[H] 30	19.4	106	27.2	165	23.1	31	24.0	332	23.7			
4 (moderately thin)	77	50.0	44	11.3	141	19.7	19	14.7	281	20.0			
5 (very thin)	43	29.1	13	3.3	50	7.0	9	7.0	115	8.3			

Abbreviations: Chi: chi-square test statistic across the four study groups, unless otherwise noted. F: F statistic. FAS: fetal alcohol syndrome. Hgt: height. P: p-value. PFAS: partial FAS. PFL: palpebral fissure length. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. SD: standard deviation. SE/AE: Static encephalopathy/alcohol exposed. Wgt: weight. Wks: weeks.
Notations: A. Numerator degrees of freedom = 3; denominator df = total sample size minus 4. B. The Duncan multiple comparisons range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at $p < 0.05$. C. All 55 Rank 1 growths are PFAS. D. All 69 Rank 3 faces are PFAS; E. 25 too young to rule out CNS Rank 3 (< 8yrs). F. All 7 are too young to rule out CNS Rank 3 (<8yrs). G. All 30 Rank 3 philtrums are PFAS. H. All 30 Rank 3 lips are PFAS.

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TABLE 5 CNS structural / neurological outcomes (4-Digit CNS Rank 4) across the four study groups.

Characteristic	FASD Diagnostic Subgroups										Statistics		
	1. 59 FAS/ 95 PFAS		2. SE/AE		3. ND/AE		4. Normal CNS/AE		Total		ANOVA		Chi-square
											Overall	Post Hoc	
	N = 154		N = 394		N = 722		N = 130		N = 1400		F (p)[A]	Duncan[B]	Chi (p)
CNS Rank in 4-Digit Code: N(valid%)													
Rank 1	0	0	0	0	0	0	130	100	130	9.3			2844(00)
Rank 2	0	0	0	0	722	100	0	0	722	51.6			
Rank 3	65	42.2	244	61.9	0	0	0	0	309	22.1			
Rank 4	89	57.8	150	38.1	0	0	0	0	239	17.1			
CNS functional Rank independent of Rank 4	N (valid%)	Age yrs mean(SD)	N (valid%)	Age yrs mean(SD)	N (valid%)	Age yrs mean(SD)	N (valid%)	Age yrs mean(SD)	N (valid%)	Age yrs mean(SD)			
Rank 1 (no dysfunction)	40 (26)	4.4 (5.8)	66 (16.8)	8.5 (8.2)	0 (0)	--	130(100)	6.7 (7.0)	236(16.9)	6.8 (7.3)			1740(00)
Rank 2 (mild dysfunction)	19 (12.3)	7.1 (5.1)	52 (13.2)	10.9 (9.5)	722(100)	8.9 (5.5)	0 (0)	--	793(56.6)	8.9 (5.9)			
Rank 3 (severe dysfunction)	95 (61.7)	11.2 (8.8)	276(70.1)	10.2 (4.5)	0 (0)	--	0 (0)	--	371(26.5)	10.5 (5.9)			
Duncan[B] comparing mean age between CNS Ranks 1,2,3: F(p)		F11.3(.00) Rank 12,3		F2.9(.06)						F26.8(.00) Rank 1,2,3			
CNS functional Rank among those with CNS Rank 4	N (valid%)	[C]Age yrs mean(SD)	N (valid%)	[C]Age yrs mean(SD)	N (valid%)	[C]Age yrs mean(SD)	N (valid%)	[C]Age yrs mean(SD)	N (valid%)	[C]Age yrs mean(SD)			
Rank 4 that is also Rank 1	40 (44.9)	[D]4.4 (5.8)	[F]66 (44.0)	8.5 (8.2)	n/a	n/a	n/a	n/a	106(44.4)	6.9 (7.6)			
Rank 4 that is also Rank 2	19 (21.3)	[E]7.1 (5.1)	[G]52(34.7)	10.9 (9.5)	n/a	n/a	n/a	n/a	71(29.7)	9.9 (8.7)			
Rank 4 that is also Rank 3	30 (33.7)	9.2 (5.0)	32 (21.4)	9.3 (3.1)	n/a	n/a	n/a	n/a	62(25.9)	9.3 (7.3)			
Duncan[B] comparing mean age between CNS Ranks 1,2,3: F(p)		7.0(.002) Rank12,23		1.3(.27)						4.0 (.02) Rank13,32			
Microcephaly: N (valid%)	69	44.8	99	25.3	0	0	0	0	168	12.1			[H]75(00)
OFC percentile: N, mean (SD)	152	24.0(28.0)	391	39.6(31.4)	715	52.0(23.8)	126	53.5(24.4)	1384	45.7(28.3)	57(00)	1,2,34	
Abnormal MRI among those Imaged: N (valid%)	7	26.9	18	30.5	0	0	0	0	25	18.1			
Seizure disorder: N (valid%)	10	6.5	32	8.1	0	0	0	0	42	3.0			
Why CNS Rank 4: N (valid%)	Of the 89 with Rank 4		Of the 150 with Rank 4						Of the 239 with Rank 4				
Microcephaly only	66	82.5	88	58.7	n/a	n/a	n/a	n/a	154	64.4			
Abnormal MRI only	2	0.3	13	8.7	n/a	n/a	n/a	n/a	15	6.3			
Seizure disorder only	7	0.9	18	12.0	n/a	n/a	n/a	n/a	25	10.5			
Microcephaly & abnormal MRI	3	0.4	0	0	n/a	n/a	n/a	n/a	3	1.3			
Microcephaly & seizures	0	0	9	6.0	n/a	n/a	n/a	n/a	9	3.8			
Abnormal MRI & seizures	2	0.3	2	1.3	n/a	n/a	n/a	n/a	4	1.7			
All 3	0	0	2	1.3	n/a	n/a	n/a	n/a	2	0.1			
Vision problems: N (valid%)	42	37.5	108	33.2	155	25.2	20	18.5	325	28.0			16(00)
Chronic hearing loss: N (valid%)	23	21.3	71	22.8	95	15.9	14	13.1	203	18.1			9.2(03)

Abbreviations: Chi2: chi-square test across the four study groups, unless otherwise noted. CNS: central nervous system. F: F statistic. FAS: fetal alcohol syndrome. Microcephaly: OFC <= -2SD. MRI: magnetic resonance image. OFC: Occipital frontal circumference. P: p-value. PFAS: partial FAS. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. SD: standard deviation. SE/AE: Static encephalopathy/alcohol exposed. Yrs: years. Notations: A. Numerator degrees of freedom = 3; denominator df = total sample size minus 4. B. The Duncan multiple comparisons range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at p < 0.05. C. Of those with Rank 4 CNS, are those with Rank 1 too young to rule-out Rank 3? D. Only 5 (12%) of the 40 with Rank 1 function are >7yrs old. E. Only 4 (21%) of the 19 with Rank 2 Function are > 7 yrs old. F) 28 (42%) of the 66 with Rank 1 function are > 7 yrs old. G) 27 (52%) of the 52 with Rank 2 function were > 7 yrs old. H) Group 1 versus Group 2.

TABLE 6 CNS Functional outcomes (4-Digit CNS Ranks 1-3) across the four study groups.

Characteristic	FASD Diagnostic Subgroups										Statistics		
	1. 59 FAS/ 95 PFAS		2. SE/AE		3. ND/AE		4. Normal CNS/AE		Total		ANOVA Overall	ANOVA Post Hoc	Chi-square2
	N = 154		N = 394		N = 722		N = 130		N = 1400		F (p) [A]	Duncan[B]	Chi (p)
CNS functional Rank: N (valid%)													
Rank 1 (no dysfunction)	40	26.0	66	16.8	0	0	130	100	236	16.9			1740 (00)
Rank 2 (mild dysfunction)	19	12.3	52	13.2	722	100	0	0	793	56.6			
Rank 3 (severe dysfunction)	95	61.7	276	70.1	0	0	0	0	371	26.5			
Domain with Significant Dysfunction: N (valid%)													
Cognition	33	36.7	96	32.2	11	2.9	0	0	140	17.5			[c]120(.00)
Adaptation	47	70.1	109	72.7	65	36.1	0	0	221	53.2			[c]51(.00)
Achievement	32	43.2	132	56.4	35	12.5	0	0	199	32.8			[c]113(.00)
Executive Function, Memory	45	58.4	124	56.1	49	17.7	0	0	218	36.0			[c]93(.00)
Language	52	50.0	174	61.3	73	16.7	0	0	299	34.2			[c]157(.00)
Motor/Sensory	27	57.4	36	36.0	51	29.1	0	0	114	35.3			
Development	38	51.4	66	50.8	64	34.6	0	0	168	38.5			[c]35(.00)
ADHD	49	43.4	149	51.7	227	45.0	0	0	425	42.8			[c]4(.13)
Intelligence (WISC) FSIQ Std: N mean (SD)	88	77.8 (13.5)	274	78.8 (14.8)	347	93.4(13.0)	22	101.3(10.6)	731	86.3(15.7)	79.2(.00)	12,3,4	
FSIQ Std <= 70: N (valid%)	26	20.0	72	19.3	4	0.6	0	0	102	8.2			144(.00)
VIQ Std: N mean (SD)	67	78.4(14.0)	222	79.1(14.3)	242	92.0(12.8)	12	102.4(13.0)	543	85.2(15.2)	46.9(.00)	12,3,4	
VIQ Std <= 70: N (valid%)	20	15.4	65	17.4	9	1.4	0	0	94	7.5			106(.00)
PIQ Std: N mean (SD)	66	78.6 (13.8)	223	81.6(16.0)	235	94.3(13.4)	11	107.0(12.6)	535	87.3 (16.2)	44.6 (.00)	12,3,4	
PIQ Std <= 70: N (valid%)	16	12.3	54	14.5	8	1.3	0	0	78	6.3			85(.00)
Perceptual Organization Std: N mean (SD)	15	82.6 (17.0)	47	84.3 (13.2)	59	93.9 (13.6)	1	93.0	122	88.8 (14.6)	8.0 (.001)	[c] 12,3	
Verbal Comprehension Std: N mean(SD)	14	82.9 (13.8)	47	83.3 (13.9)	59	94.8 (12.9)	1	95.0	121	89.0 (14.5)	11.0 (.00)	[c] 12,3	
Freedom Distractibility Std: N mean(SD)	12	79.5 (14.5)	36	79.7 (12.9)	50	91.1 (13.1)	1	90.0	99	85.3 (14.3)	9.2 (.00)	[c] 12,3	
Information Sc: N mean (SD)	47	6.1 (2.9)	138	6.0 (2.8)	161	8.5 (2.7)	9	10.4 (2.8)	355	7.3 (3.1)	24.4 (.00)	12,3,4	
Similarities Sc Score: N mean (SD)	46	7.3 (3.2)	137	6.7 (3.2)	166	9.1 (3.1)	8	10.4 (2.3)	357	8.0 (3.4)	17.5 (.00)	12,34	
Arithmetic Sc: N mean (SD)	47	4.9 (2.4)	137	6.1 (2.7)	161	7.9 (2.5)	7	9.6 (3.7)	352	6.8 (2.8)	23.9 (.00)	12,3,4	
Vocabulary Sc: N mean (SD)	46	6.0 (3.4)	143	6.8 (3.1)	166	8.9 (2.8)	8	10.5 (3.2)	363	7.7 (3.2)	20.8 (.00)	12,34	
Comprehension Sc: N mean (SD)	44	6.5 (3.1)	132	6.5 (3.1)	159	8.9 (3.2)	7	10.6 (3.8)	342	7.7 (3.4)	17.5 (.00)	12,34	
Digit Span Sc: N mean (SD)	35	6.3 (2.9)	93	6.5 (2.6)	116	8.2 (2.6)	4	10.0 (6.2)	248	7.3 (2.8)	9.2 (.00)	123,34	
Picture Completion Sc: N mean (SD)	46	6.9 (3.3)	139	7.6 (2.8)	162	9.5 (2.9)	7	12.6 (3.2)	354	8.5 (3.1)	20.0 (.00)	12,3,4	
Picture Arrangement Sc: N mean (SD)	37	6.3 (3.2)	119	7.1 (3.6)	141	8.8 (3.1)	7	11.3 (3.1)	304	7.9 (3.5)	11.1 (.00)	12,23,4	
Block Design Sc: N mean (SD)	47	6.3 (3.3)	146	6.9 (3.4)	170	8.9 (3.2)	8	10.9 (2.4)	371	7.8 (3.4)	15.2 (.00)	12,3,4	
Object Assembly Sc: N mean (SD)	44	7.5 (3.3)	125	7.8 (3.6)	146	9.1 (2.9)	8	11.6 (2.8)	323	8.5 (3.3)	7.9 (.00)	123,4	
Coding Sc: N mean (SD)	35	5.8 (3.2)	113	6.5 (3.6)	142	8.3 (3.3)	6	8.8 (2.6)	296	7.4 (3.5)	8.8 (.00)	12,234	
Mazes Sc: N mean (SD)	6	3.8 (1.9)	25	6.6 (3.0)	31	9.0 (3.3)	1	15.0 (--)	63	7.7 (3.6)	8.0 (.00)	--	
Visual-Motor/Sensory QNST R:mean(SD)	28	37.2(16.9)	82	32.8(15.7)	114	24.2(13.2)	9	16.2(7.0)	233	28.5(15.4)	11.1 (.00)	12,3,4	
VMI Std: mean (SD)	37	77.3(11.4)	76	80.6(13.0)	140	89.6(10.2)	11	95.9(12.4)	264	85.5(12.5)	20.4 (.00)	12,3,4	
SSP Total = Definite Difference: N (valid%)	18	75.0	13	54.2	44	81.5	0	0	75	73.8			[c]6.4(.04)
Executive Function/Memory RCFT Copy R: mean(SD)	13	15.2(9.6)	40	18.8(9.9)	42	25.5(9.2)	3	32.7(1.5)	98	21.6(10.3)	7.0 (.00)	12,23,34	
RCFT 3min recall T: mean (SD)	13	25.2(5.6)	35	32.0(13.2)	39	42.5(14.7)	3	43.0(2.6)	90	36.0(14.4)	7.7 (.00)	12,234	
RCFT 30min recall T: mean (SD)	4	31.8(5.0)	13	28.1(13.0)	20	38.4(15.1)	2	45.5(2.1)	39	34.6(14.1)	2.0 (.13)	--	

Abbreviations: ADHD: attention deficit hyperactivity disorder. Chi: chi-square test statistic across the four study groups, unless otherwise noted. F: F statistic. FAS: fetal alcohol syndrome. FSIQ: full scale IQ. P: p-value. PFAS: partial FAS. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. PIQ: Performance IQ. QNST: Quick Neurological Screening Test[45]. RCFT: Rey Complex Figure Test[42]. R: raw score. Sc: scaled score. SD: standard deviation. SE/AE: Static encephalopathy/alcohol exposed. SSP: Short Sensory Profile[46]. Std. standard score. T: t score. VIQ: Verbal IQ. VMI: Beery Buktenica Developmental Test of Visual Motor Integration[41]. WISC: Wechsler Intelligence Scale for Children[40]. Notations: A. Numerator degrees of freedom = 3; denominator df = total sample size minus 4. B. The Duncan multiple comparisons range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at $p < 0.05$. C. Only groups 1, 2 and 3 are compared.

TABLE 7 Child Behavior Check List (CBCL/ 6-18) outcomes (see Figure 2) among the 516 patients administered a CBCL when they were between 6 and 18 years of age.

Characteristic	FASD Diagnostic Subgroups										Statistics	
	1. 59 FAS/ 95 PFAS		2. SE/AE		3. ND/AE		4. Normal CNS/AE		Total		ANOVA Overall	ANOVA Post Hoc
	N = 154		N = 394		N = 722		N = 130		N = 1400		F (p)[A]	Duncan[B]
Problems: T-score[C]	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)		
Internalizing	51	63.4(10.1)	154	64.5(10.9)	270	65.6(10.9)	25	60.8(14.1)	500	64.8(11.0)	1.9 (.14)	--
Externalizing	51	69.1(9.9)	154	69.6(10.9)	270	70.8(10.3)	25	60.3(13.2)	500	69.8(10.8)	7.6 (.000)	123,4
Total	51	71.4(8.9)	154	71.3(9.3)	270	72.1(9.0)	25	61.9(12.7)	500	71.3(9.5)	9.1 (.000)	123,4
Syndrome Scales: T-score[D]												
Anxious/Depressed	51	63.0(11.3)	153	64.0(9.9)	269	64.9(10.9)	25	62.6(12.1)	498	64.3(10.7)	0.8 (.53)	--
Withdrawn/Depressed	50	62.4(8.6)	153	64.6(11.2)	269	65.0(11.1)	25	63.1(12.4)	497	64.5(10.9)	0.9 (.42)	--
Somatic Complaints	51	60.0(9.3)	153	60.6(10.8)	269	61.8(10.0)	25	57.9(7.0)	498	61.0(10.1)	1.6 (.19)	--
Social Problems	50	72.0(12.0)	153	69.7(10.2)	269	68.5(10.2)	25	59.1(10.3)	497	68.8(10.7)	9.3 (.00)	123,4
Thought Problems	50	70.7(10.7)	153	69.1(10.6)	270	68.4(10.2)	25	61.6(8.8)	498	68.5(10.4	4.6 (.003)	123,4
Attention Problems	51	75.5(11.9)	153	75.7(11.0)	270	74.3(11.4)	25	64.2(13.1)	497	74.4(11.6)	7.6 (.000)	123,4
Rule-Breaking Behavior	51	67.9(8.9)	153	67.5(10.2)	269	69.7(10.0)	25	61.5(11.4)	498	68.4(10.2)	6.0 (.001)	123,4
Aggressive Behavior	50	70.2(13.1)	153	71.7(12.1)	269	72.0(12.2)	25	61.6(12.5)	497	71.2(12.4)	5.7 (.001)	123,4
Competence Scales: T-score [E]												
Activities	44	41.5(8.9)	135	42.8(8.8)	220	44.3(7.7)	18	46.1(7.2)	417	43.6(8.2)	2.5 (.05)	123,234
Social	44	36.0(9.2)	130	34.5(9.1)	211	36.4(9.8)	18	40.3(11.9)	403	35.9(9.7)	2.3 (.07)	123,34
School	37	28.3(6.4)	111	29.4(6.0)	181	31.9(6.2)	13	38.9(9.0)	342	31.0(6.6)	12.7 (.00)	12,23,4
Total	37	31.8 (10.0)	109	32.4 (8.2)	172	35.1 (7.6)	13	40.3 (9.4)	331	34.0 (8.4)	5.9 (.003)	123,4

Abbreviations: F: f-statistic. FAS: fetal alcohol syndrome. P: p-value. PFAS: partial FAS. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. SD: standard deviation. SE/AE: Static encephalopathy/alcohol exposed. Notations: A. Numerator degrees of freedom = 3; denominator df = total sample size minus 4. B. The Duncan multiple comparisons range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at $p < 0.05$. C. Borderline clinical range (T score 60-63). Clinical range (T score > 63). D. Borderline clinical range (T score 65-69). Clinical range (T score > 69). E. (Activities, Social, School): Borderline clinical range (T score 31-35). Clinical range (T score <31); (Total): Borderline clinical range (T score 37-40). Clinical range (T score <37).

TABLE 8 Proportion of patients classified by the pediatrician as 'significantly delayed/impaired' across a spectrum of behaviors at the conclusion of a 2-hour, structured caregiver interview administered jointly by the pediatrician and psychologist during the FASD diagnostic evaluation (see Figure 3).

Patient Behaviors addressed in Caregiver Interview	FASD Diagnostic Subgroups										Statistic
	1. 59 FAS/ 95 PFAS		2. SE/AE		3. ND/AE		4. Normal CNS/AE		Total		Chi-square Groups 1,2,3
	N = 154		N = 394		N = 722		N = 130		N = 1400		Chi (p)
Domain Behavior	N	Valid %	N	Valid %	N	Valid %	N	Valid %	N	Valid %	
Planning											
Needs considerable help organizing daily tasks	24	24.0	63	22.4	92	20.2	5	10.6	184	20.8	2.9 (.57)
Cannot organize time	21	31.3	56	29.0	59	20.6	5	20.0	141	24.7	10.2 (.04)
Does not understand concept of time	17	31.5	39	25.7	48	20.2	1	3.3	105	22.2	11.8 (.02)
Difficulty carrying out multistep tasks	27	26.5	61	21.4	88	19.1	5	10.4	181	20.2	8.2 (.09)
Behavioral Regulation/Sensory Motor Integration:											
Poor management of anger/tantrums	24	18.8	74	22.2	127	19.7	8	7.9	233	19.3	7.9 (.10)
Mood swings	19	16.7	54	18.1	102	18.1	4	4.5	179	16.8	4.9 (.30)
Impulsive	28	24.8	87	27.8	137	22.9	9	11.0	261	23.6	6.7 (.15)
Compulsive	7	8.6	19	8.3	29	6.6	1	1.5	56	6.9	2.4 (.67)
Perseverative	18	18.8	18	7.7	42	9.5	1	1.6	79	9.4	11.5 (.02)
Inattentive	28	24.3	76	23.3	113	18.9	8	9.4	225	20.0	8.8 (.07)
Inappropriate activity level	27	24.5	70	26.0	92	17.7	2	3.3	191	19.9	8.8 (.07)
Lying/stealing	16	14.4	52	18.2	63	11.8	5	5.6	136	13.3	7.3 (.12)
Unusual high/low reactivity to sound/touch/light	27	27.6	42	18.4	60	15.6	4	6.0	133	17.1	10.2 (.03)
Abstract Thinking/Judgment:											
Poor judgment	28	31.1	81	29.7	98	20.5	4	8.2	211	23.7	18.2 (.00)
Cannot be left alone	19	26.4	56	27.3	64	18.4	3	8.6	142	21.5	19.4 (.00)
Concrete, unable to think abstractly	17	25.8	55	30.9	32	12.6	1	4.8	105	20.2	65.6 (.00)
Memory/Learning/Information Processing:											
Poor memory, inconsistent retrieval of learned information	33	28.0	77	23.6	72	13.4	18	22.5	200	18.8	26.7 (.00)
Slow to learn new skills	21	17.2	62	19.7	41	7.	1	1.1	125	11	78.9 (.00)
Does not seem to learn from past experiences	21	22.6	72	26.0	96	18.9	4	6.3	193	20	7.3 (.12)
Problems recognizing consequences of actions	21	21.9	75	28.2	97	19.6	4	6.9	197	21.5	8.2 (.08)
Problems w/information processing speed/accuracy	19	21.6	54	21.9	42	10.1	1	1.6	116	14.3	97.0 (.00)
Spatial Memory:											
Gets lost easily. Difficulty navigating from A to B	10	16.1	20	13.1	13	5.2	0	0	43	8.6	25.5 (.00)
Social Skills and Adaptive Behavior:											
Behaves at a level notably younger than chronological age	32	27.8	72	21.9	60	10.7	3	3.4	167	15.3	50.8 (.00)
Poor social/adaptive skills	30	25.2	70	20.8	91	14.6	4	4.3	195	16.7	18.3 (.00)
Motor/Oral Motor Control:											
Poor/delayed motor skills	20	16.5	34	11.0	21	3.7	0	0	75	6.9	61.4 (.00)
Poor balance	20	20.8	30	12.8	17	3.7	0	0	67	7.8	65.0 (.00)

Abbreviations: Chi: chi-square test statistic across Groups 1, 2 and 3. FAS: fetal alcohol syndrome. P: p-value. PFAS: partial FAS. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. SE/AE: Static encephalopathy/alcohol exposed. Notations: Not all patients are old enough to demonstrate each of the behaviors listed above. Thus the valid % reflects the proportion of patients with significant impairment among those old enough to demonstrate the behavior.

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Profile of the first 1,400 patients receiving diagnostic evaluations for fetal alcohol spectrum disorder at the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network

TABLE 9 Alcohol exposure history across the four study groups.

Characteristic	FASD Diagnostic Subgroups										Statistics		
	1. 59 FAS/ 95 PFAS		2. SE/AE		3. ND/AE		4. Normal CNS/AE		Total		ANOVA		Chi-square
											Overall	Post Hoc	
	N = 154		N = 394		N = 722		N = 130		N = 1400		F (p)[A]	Duncan[B]	Chi (p)
Prenatal Alcohol Rank: N (valid%)													
Rank 1: Confirmed Absent	0	0	0	0	0	0	0	0	0	0			27 (.00)
Rank 2: Unk.	[C]7	4.5	0	0	0	0	0	0	7	0.5			
Rank 3: Confirmed; amount moderate or unk.	60	39.0	164	41.6	346	47.9	56	43.1	626	44.7			
Rank 4: Confirmed; amount high	87	56.5	230	58.4	376	52.1	74	56.9	767	54.8			
Before Pregnancy: N, mean (SD)													
Ave # drinks per drinking occasion	50	8.2(7.0)	162	9.8(10.1)	308	9.3(10.1)	67	10.9(12.8)	587	9.5(10.2)	0.8 (.50)		
Max # drinks per drinking occasion	52	12.0(9.4)	156	16.0(15.8)	264	14.8(14.7)	64	15.4(20.3)	536	14.9(15.4)	0.9 (.44)		
Ave # drinking days per week	72	5.5(2.0)	206	4.4(2.2)	373	4.7(2.2)	82	4.8(2.2)	733	4.7(4.8)	4.9(.002)	1,234	
Type of alcohol consumed: N (valid%)													
beer	63	40.9	140	35.5	273	37.8	55	42.3	531	37.9			2.6 (.46)
wine	20	13.0	58	14.7	100	13.9	19	14.6	197	14.1			0.3 (.96)
liquor	45	29.2	122	31.0	197	27.3	32	24.6	396	28.3			2.7 (.44)
During Pregnancy: N, mean (SD)													
Ave # drinks per drinking occasion	54	8.0(7.3)	176	8.2(8.4)	331	8.6(10.2)	69	9.1(14.2)	630	8.5(10.0)	0.2 (.89)		
Max # drinks per drinking occasion	56	12.5(10.0)	169	12.9(11.0)	275	13.3(13.9)	65	10.6(9.9)	565	12.8(12.3)	0.8 (.48)		
Ave # drinking days per week	81	5.6(2.1)	227	4.3(2.4)	409	4.4(2.3)	86	4.4(2.3)	803	4.5(2.3)	7.1(.000)	1,234	
Type of alcohol consumed: N (valid%)													
beer	64	41.6	153	38.8	280	38.8	60	46.2	557	39.8			2.9 (.41)
wine	22	14.3	58	14.7	102	14.1	18	13.8	200	14.3			0.1 (.99)
liquor	42	27.3	114	28.9	197	27.3	31	23.8	384	27.4			1.3 (.73)
Trimester of Alcohol Use: N (valid%)													[E] 4.2 (.24)
1st only	17	13.8	55	17.2	71	12.4	11	9.7	154	13.6			
1st and 2nd only	17	13.8	38	11.9	61	10.6	19	16.8	135	12.0			
[D] All 3	88	71.5	214	66.9	418	72.9	74	65.5	794	70.3			
Had an alcohol use problem: N (valid%)	127	93.4	315	86.5	622	93.1	113	91.6	1177	91.2			14 (.00)
Diagnosed with alcoholism: N (valid%)	90	82.6	241	76.3	545	79.8	102	87.2	887	79.8			7.3 (.06)
Received alcohol treatment: N (valid%)	86	78.9	214	70.4	412	72.8	95	81.2	807	73.6			6.9 (.08)
Source of alcohol information: N (valid%)													
Birth mother report	51	35.9	170	43.8	300	42.5	58	45.0	597	42.5			3.2 (.79)
Person who directly observed birth mother	55	38.7	133	34.3	248	35.0	44	34.1	480	35.1			
Other Source (med/legal/social reports)	36	25.4	85	21.9	160	22.6	27	20.9	308	22.5			

Abbreviations:: Chi: chi-square test statistic across Groups 1, 2 and 3, unless otherwise noted. FAS: fetal alcohol syndrome. P: p-value. PFAS: partial FAS. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. SE/AE: Static encephalopathy/alcohol exposed. Unk: unknown. Notations: A. Numerator degrees of freedom = 3; denominator df = total sample size minus 4. B. The Duncan multiple comparisons range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at $p < 0.05$. C. All 7 unknown alcohol exposures have a full FAS diagnosis. D. When FAS/PFAS are split, 35 (81.4%) of the FAS group were exposed all 3 trimesters, compared to 53 (66.3%) of the PFAS group. E. All 3 trimesters versus less than 3 trimesters.

Profile of the first 1,400 patients receiving diagnostic evaluations for fetal alcohol spectrum disorder at the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network

TABLE 10 Other prenatal and postnatal adverse exposures and events across the four study groups.

Characteristic	FASD Diagnostic Subgroups										Statistics		
	1. 59 FAS/ 95 PFAS		2. SE/AE		3. ND/AE		4. Normal CNS/AE		Total		ANOVA Overall	ANOVA Post Hoc	Chi-square
	N = 154		N = 394		N = 722		N = 130		N = 1400		F (p)[A]	Duncan[B]	Chi (p)
Prenatal Rank from 4-Digit Code: N (valid%)													
Rank 1: No risk	2	1.3	6	1.6	4	0.6	0	0	12	0.9			7.8 (.05)
Rank 2: Unknown Risk	27	17.9	55	14.2	89	12.4	19	14.6	190	13.7			
Rank 3: Some Risk	102	67.5	283	73.3	574	79.9	101	77.7	1060	76.5			
Rank 4: High Risk	20	13.2	42	10.9	51	7.1	10	7.7	123	8.9			
No prenatal care: N (valid%)	32	42.7	59	30.7	106	30.0	18	26.1	215	31.2			15.5 (.02)
Prenatal complications: N (valid %)	28	37.3	82	41.2	126	34.0	23	28.8	259	35.7			4.9 (.18)
Maternal learning disabilities: N (valid%)	57	56.4	168	60.6	291	59.5	47	50.0	563	58.6			3.7 (.29)
Paternal learning disabilities: N (valid%)	22	43.1	97	53.9	165	54.3	24	38.7	308	51.6			6.8 (.08)
Other syndromes All	2	1.3	10	2.5	4	0.5	2	1.5	18	1.3			8.0 (.05)
Binder	0	0	0	0	1	0.1	0	0	1	0.1			
Hemifacial microsomia	0	0	1	0.3	1	0.1	0	0	2	0.1			
Kabuki Makeup	0	0	1	0.3	0	0	0	0	1	0.1			
Marfan	0	0	1	0.3	0	0	0	0	1	0.1			
Schprintzen	0	0	1	0.3	0	0	0	0	1	0.1			
Sticklers	1	0.6	0	0	2	0.3	1	0.8	4	0.3			
Williams	0	0	1	0.3	0	0	1	0.8	2	0.1			
Kleinfelters	0	0	1	0.3	0	0	0	0	1	0.1			
Neurofibromatosis	0	0	1	0.3	0	0	0	0	1	0.1			
Amniotic band sequence	0	0	1	0.3	0	0	0	0	1	0.1			
Moebius sequence	0	0	2	0.5	0	0	0	0	2	0.1			
Down syndrome	1	0.6	0	0	0	0	0	0	1	0.1			
Other adverse prenatal exposures Any exposure	104	92.0	271	88.9	499	96.0	101	94.4	975	93.3			17.8 (.00)
Tobacco	84	57.1	238	61.5	455	63.6	84	64.6	861	62.4			2.6 (.46)
Marijuana	36	24.5	139	35.9	279	39.0	49	37.7	503	36.5			11.2 (.01)
Crack/Cocaine	58	39.5	124	32.0	279	39.0	60	46.2	521	37.8			9.9 (.02)
methamphetamines	15	10.2	26	6.7	52	7.3	9	6.9	102	7.4			2.0 (.57)
LSD/acid	6	4.1	15	3.9	23	3.2	3	2.3	47	3.4			[C] (.62)
Dilantin	1	0.7	1	0.3	6	0.8	0	0	8	0.6			[C] (1.0)
Postnatal Rank from 4-Digit Code: N(valid%)													
Rank 1: No risk	7	4.6	11	2.8	29	4.1	7	5.4	54	3.9			32.2 (.00)
Rank 2: Unknown Risk	18	11.9	42	10.8	87	12.2	33	25.4	180	13.0			
Rank 3: Some Risk	61	40.4	166	42.7	304	42.5	61	46.9	592	42.7			
Rank 4: High Risk	65	43.0	170	43.7	296	41.3	29	22.3	560	40.4			
Perinatal difficulties: N (valid%)	66	59.5	188	59.9	282	49.4	47	44.3	583	52.9			[D]17.7(.00)
Days in the birth hospital: N mean (SD)	57	9.6 (14.7)	155	8.1 (19.3)	256	7.0 (15.4)	43	3.8 (4.8)	521	7.4 (16.1)			1.3 (.28)
Physical abuse: N (valid%)	47	36.7	122	36.6	210	35.2	22	19.6	401	34.3			13.1 (.04)
Sexual abuse: N (valid%)	26	22.0	85	26.6	147	25.6	5	4.7	263	23.5			26.4 (.00)
Neglect: N (valid%)	86	65.6	235	67.3	399	63.9	65	56.5	785	64.4			4.6 (.21)
Total # of home placements: N mean (SD)	119	2.7 (2.3)	310	3.1 (3.5)	533	2.9 (3.3)	84	2.3 (1.3)	1046	2.9 (3.1)	1.5(.21)	--	

Abbreviations:: Chi: chi-square test statistic across the 4 study groups unless otherwise noted. FAS: fetal alcohol syndrome. P: p-value. PFAS: partial FAS. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. SD: standard deviation. SE/AE: Static encephalopathy/alcohol exposed. Notations: A. Numerator degrees of freedom = 3; denominator df = total sample size minus 4. B. The Duncan multiple comparisons range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at $p < 0.05$. C. Fisher Exact Test: FASD groups versus Group 4. D. High risk versus all other risk groups.

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TABLE 11 Mental health disorders reported in the medical records of the 1,064 patients 5 or more years of age at the time of the FASD diagnostic evaluation across the four study groups.

Characteristic	FASD Diagnostic Subgroups										Statistics
	1. 59 FAS/ 95 PFAS		2. SE/AE		3. ND/AE		4. Normal CNS/AE		Total		Chi-square
	N = 154		N = 394		N = 722		N = 130		N = 1400		Chi (p)
Mental Health Disorders: N (valid%)											
One or more disorders	73	71.6	180	84.1	293	74.0	10	28.6	546	74.5	56 (.00)
ADD/ADHD	53	59.6	161	59.9	233	55.2	0	0	447	53.9	148 (.00)
Adjustment Disorder	4	2.6	8	2.0	29	4.0	3	2.3	44	3.1	3.9 (.27)
Antipersonality Disorder	0	0	0	0	1	0.1	0	0	1	0.1	--
Anxiety Disorder	2	1.3	10	2.5	8	1.1	0	0	20	1.4	5.8 (.12)
Reactive Attachment Disorder	6	3.9	19	4.8	27	3.7	2	1.5	54	3.9	2.9 (.41)
Bipolar/Manic Depression	4	2.6	10	2.5	13	1.8	3	2.3	30	2.1	0.8 (.85)
Conduct Disorder	2	1.3	16	4.1	24	3.3	1	0.8	43	3.1	5.3 (.15)
Depression	7	4.5	23	5.8	32	4.4	2	1.5	64	4.6	4.2 (.24)
Dysthymic Disorder	3	1.9	7	1.8	23	3.2	2	1.5	35	2.5	3.0 (.39)
Obsessive Compulsive Disorder	1	0.6	6	1.5	2	0.3	0	0	9	0.6	6.5 (.09)
Oppositional Defiant Disorder	8	5.2	39	9.9	72	10.0	1	0.8	120	8.6	15.0 (.00)
Post Traumatic Stress Disorder	10	6.5	32	8.1	49	6.8	4	3.1	95	6.8	3.9 (.27)
Suicidal	2	1.3	3	0.8	5	0.7	0	0	10	0.7	1.7 (.64)

Abbreviations:: Chi: chi-square test statistic across the 4 study groups. FAS: fetal alcohol syndrome. P: p-value. PFAS: partial FAS. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. SE/AE: Static encephalopathy/alcohol exposed.

TABLE 12 Patient Satisfaction Survey outcomes from the University of Washington FAS DPN Clinic.

Characteristic	FASD Diagnostic Subgroups										Statistics
	1. 43 FAS/ 64 PFAS		2. SE/AE		3. ND/AE		4. Normal CNS/AE		Total		Chi-square
	N = 107		N = 248		N = 487		N = 88		N = 930		Chi (p)
Question on Patient Satisfaction Survey: N (valid%)											
1. Did we provide you with information you needed and were unable to get elsewhere?											
Yes	30	96.8	73	93.6	122	88.4	19	90.5	244	91.0	3.9 (.28)
2. Was the explanation of the patient's diagnosis easy to understand?											
Yes	36	90.0	71	81.6	133	85.8	22	91.7	262	85.6	2.5 (.48)
3. When you left Clinic, we recommended that you contact certain people and services to help you. How successful were you at finding these people and services?											
Very successful	15	46.9	33	55.0	55	44.0	9	52.9	112	47.9	3.7 (.30)
Somewhat successful	11	34.4	18	30.0	48	38.4	3	17.6	80	34.2	
4. If you were able to find the people and services we recommended to you, were they able to meet your needs?											
Yes, met all my needs	7	36.8	20	44.4	34	34.3	10	66.7	71	39.9	6.8 (.08)
Yes, met some of my needs	10	52.6	16	42.2	46	46.5	3	20.0	78	43.8	
No, they met none of my needs	1	5.3	3	6.7	6	6.1	0	0	10	5.6	
I was not able to find the people/services	1	5.3	3	6.7	13	13.1	2	13.3	19	10.7	
5. Would you recommend the FAS Clinic to other families with similar needs?											
Yes	32	100	75	98.7	143	98.6	21	100	271	98.9	0.7 (.87)
Duration of wait to get a diagnostic appointment. (yrs): mean SD	.53	.65	.59	.68	.56	.57	.49	.38	.56	.60	1.1 (.37)

Abbreviations:: Chi: chi-square test statistic across the 4 study groups. FAS: fetal alcohol syndrome. P: p-value. PFAS: partial FAS. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. SD: standard deviation. SE/AE: Static encephalopathy/alcohol exposed.

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Profile of the first 1,400 patients receiving diagnostic evaluations for fetal alcohol spectrum disorder at the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network

TABLE 13 Selected contrasts between races.

Characteristic	Race (recorded as one race)										Statistics		
	1. Caucasian		2. Black		3. American Indian or Alaskan Native		4. Other (including mixed race)		Total		ANOVA		Chi-square
											Overall	Post Hoc	
	N = 684		N = 92		N = 115		N = 509		N = 1400		F (p)[A]	Duncan[B]	Chi (p)
FASD Diagnostic Group: N (valid%) 1. FAS/PFAS	87	12.7	17	18.5	6	5.2	44	8.6	154	11.0			30.1 (.00)
2. SE/AE	182	26.6	19	20.7	48	41.7	145	28.5	394	28.1			
3. ND/AE	357	52.2	45	48.9	57	49.6	263	51.7	722	51.6			
4. Normal CNS/AE	58	8.5	11	12.0	4	3.5	57	11.2	130	9.3			
Growth Rank: N (valid%) 1	436	63.7	60	65.2	87	75.7	340	66.8	923	65.9			12.9 (.17)
2	95	13.9	15	16.3	10	8.7	82	16.1	202	14.4			
3	88	12.9	12	13.0	10	8.7	54	10.6	164	11.7			
4	65	9.8	5	5.4	8	7.0	33	6.5	111	7.9			
Face Rank : N (valid%) 1	155	22.7	21	22.8	24	20.9	158	31.0	358	25.6			38.1 (.00)
2	372	54.4	46	50.0	79	68.7	275	54.0	772	55.1			
3	77	11.3	17	18.5	10	8.7	40	7.9	144	10.3			
4	80	11.7	8	8.7	2	1.7	36	7.1	126	9.0			
CNS Functional Rank: N (valid%) 1	106	15.5	20	21.7	12	10.4	98	19.3	236	16.9			14.7 (.02)
2	397	58.0	49	53.3	59	51.3	288	56.6	793	56.6			
3	181	26.5	23	25.0	44	38.3	123	24.2	371	26.5			
CNS Structural/Neurological Rank: N (valid%) 4	124	18.1	16	17.4	14	12.2	85	16.7	239	17.1			2.5 (.47)
Alcohol Rank : N (valid%) 1	0	0	0	0	0	0	0	0	0	0			23.5 (.00)
2	5	0.7	0	0	0	0	0	0	0	0			
3	278	40.6	39	42.4	39	33.9	270	53.0	626	44.7			
4	401	58.6	53	57.6	76	66.1	237	46.6	767	54.8			
Alcohol Use Before Pregnancy: N, mean (SD)													
Ave # drinks per drinking occasion	302	7.7(6.2)	45	8.5(6.9)	48	16.8(15.2)	192	10.8(13.1)	587	9.5(10.2)	13.3(.00)	124,3	
Max # drinks per drinking occasion	266	13.3(13.9)	43	12.7(9.1)	44	22.5(17.5)	183	16.0(17.4)	536	14.9(15.4)	5.2(.001)	124,3	
Ave # drinking days per week	383	4.7(2.2)	53	5.3(2.2)	55	4.1(2.3)	242	4.6(2.2)	733	4.7(2.2)	3.1 (.03)	341,12	
Alcohol Use During Pregnancy: N, mean (SD)													
Ave # drinks per drinking occasion	325	7.3(7.2)	45	8.2(6.2)	49	12.9(10.8)	211	9.4(13.4)	630	8.5(10.0)	5.4(.001)	124,3	
Max # drinks per drinking occasion	282	11.6(11.7)	41	13.4(8.2)	45	19.3(14.4)	197	12.9(13.0)	565	12.8(12.3)	5.1(.002)	124,3	
Ave # drinking days per week	415	4.6(2.3)	57	5.7(1.9)	57	3.6(2.3)	274	4.4(2.3)	803	4.5(2.3)	8.9(.00)	3,41,12	
Drank only in 1st trimester: N (valid%)	67	12.1	6	7.8	20	20.2	61	15.3	154	13.6			8.0 (.05)
Drank all 3 trimesters: N (valid%)	395	71.2	59	76.6	65	65.7	275	69.1	794	70.3			3.0 (.40)
Had an alcohol use problem: N (valid%)	569	90.5	66	82.5	107	94.7	435	92.8	1177	91.2			11.1(.01)
Diagnosed with alcoholism: N (valid%)	431	78.6	41	62.1	95	90.5	320	81.6	887	79.8			21.5 (.00)
Received alcohol treatment: N (valid%)	383	70.8	43	63.2	79	78.2	302	78.2	807	73.6			11.3 (.01)
Other adverse exposures in pregnancy: N (valid %)	488	92.6	77	96.3	65	87.8	345	94.8	975	93.3			6.3 (.09)
Child's age at diagnosis (yrs): N mean (SD)	684	9.3(6.9)	92	8.3(4.4)	115	9.5(5.5)	509	8.6(5.8)	1400	9.0(6.2)	2.2(.09)	--	
Mom's age(yr) at child's diagnosis: N mean (SD)	579	35.7(9.5)	73	35.1(6.1)	86	35.9(8.0)	412	33.4(7.9)	1147	34.8(8.7)	5.9(.001)	123,4	
Mom's age(yr) at child's birth: N mean (SD)	576	26.4(6.5)	73	26.7(5.3)	86	26.5(6.1)	412	24.9(6.1)	1147	25.9(6.3)	5.3(.001)	123,4	
Parity of index child: N mean (SD)	570	2.5 (1.5)	77	3.2 (1.8)	99	3.3 (2.1)	410	2.8 (1.8)	1156	2.7 (1.7)	7.8 (.00)	14,23	

Abbreviations: Chi: chi-square test statistic across the 4 racial groups. FAS: fetal alcohol syndrome. P: p-value. PFAS: partial FAS. ND/AE: Neurodevelopmental disorder/alcohol exposed. Normal CNS/AE: No central nervous system abnormalities/alcohol exposed. SD: standard deviation. SE/AE: Static encephalopathy/alcohol exposed. Notations: A. Numerator degrees of freedom = 3; denominator df = total sample size minus 4. B. The Duncan multiple comparisons range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at $p < 0.05$.

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Observation of Classroom Social Communication: Do Children With Fetal Alcohol Spectrum Disorders Spend Their Time Differently Than Their Typically Developing Peers?

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Purpose: In this research, the authors examined how social communication profiles during classroom activities differed between children with fetal alcohol spectrum disorders (FASD) and typically developing pair-matched peers.
Method: Twelve pairs of children were observed in their classrooms 20 min a day for 4 days across 2 weeks. Coders documented classroom social communication by recording performance on handheld computers using the Social Communication Coding System (L. B. Olswang, L. Svensson, T. E. Coggins, J. Beilinson, & A. L. Donaldson, 2006). The Social Communication Coding System consists of 6 behavioral dimensions (prosocial/engaged, passive/disengaged, irrelevant, hostile/coercive, assertive, and adult seeking) that account for all verbal and nonverbal productions during a specified timeframe. The frequency of occurrence and duration of each dimension (as measured by proportion of time and average length of time spent performing each dimension) were recorded.
Results: Children with FASD had significantly more occurrences of passive/disengaged and irrelevant behavior, and the proportion and average length of time in these behaviors were larger and longer than those of their peers. Further, children with FASD had significantly more occurrences of prosocial/engaged behavior; however, the proportion and average length of time that they spent being prosocial were smaller and shorter than those of their peers.
Implications: Results suggest children with mild FASD performed differently than their peers in regard to classroom social communication, which was consistent with parent and teacher behavioral reports.

KEY WORDS: fetal alcohol syndrome, observation, school-age children, elementary schools

School-age children who have been diagnosed with fetal alcohol spectrum disorders are frequently noted to have difficulty interacting with peers in classroom situations. Teachers as well as parents have expressed concerns about social communication for these children, along with their other behavioral and academic problems (see, e.g., Jacobson & Jacobson, 2002, for a review). Yet, for these children, the nature of the social communication problems has been difficult to portray and even more challenging to document. Standardized tests do not capture the nature of the problems, and teacher ratings yield a more global view of performance. Researchers who are interested in social

communication that occurs during dynamic, interactive events in natural contexts have long been vigorous advocates of using authentic, real-time observation (Damico, 1992; Dodge, McClaskey, & Feldman, 1985; Fujiki, Brinton, Isaacson, & Summers, 2001; Lund & Duchan, 1993; Olswang, Coggins, & Timler, 2001; Prutting & Kirchner, 1987; Rice, Sell, & Hadley, 1990). Continuous recording of ongoing verbal and nonverbal behaviors offers an opportunity to document not only individual, momentary behaviors quantified as frequency of occurrence but also behavior states or behavioral dimensions quantified using duration measures (Bakeman & Gottman, 1997; Olswang, Coggins, & Svensson, 2007; Olswang, Svensson, Coggins, Beilinson, & Donaldson, 2006). For children who are at risk for social communication problems, this perspective can provide a unique and valuable insight into classroom performance as the children interact with others. In the present study, we examined the social communication of children with fetal alcohol spectrum disorders and matched peers by documenting frequency of occurrence and duration of behavioral dimensions as they were observed in classroom settings. The purpose is to document the social communication profile of children with fetal alcohol spectrum disorders and to determine whether their profile differs from that of matched, typically developing peers.

Prenatal Alcohol Exposure and Social Communication Problems

Fetal Alcohol Spectrum Disorders

Children with prenatal alcohol exposure range in their diagnoses, from the full diagnosis of fetal alcohol syndrome (FAS) to the classification of alcohol-related neurodevelopmental disorders (ARND; Stratton, Howe, Battaglia, & the Committee to Study Fetal Alcohol Syndrome, Institute of Medicine, 1996). The label *fetal alcohol spectrum disorders (FASD)* has been used to cover this range. At one end of the continuum, FAS is characterized by growth deficiency, a unique set of minor facial anomalies, documented central nervous system (CNS) structural and/or functional abnormality, and confirmed prenatal alcohol exposure. Children with FAS may demonstrate an array of neurobehavioral problems, including cognitive, social, and language deficits that range in severity and that challenge the children's success in school and beyond. At the other end of the continuum, children with ARND are known to have been exposed to alcohol prenatally, yet they do not show the growth or facial features associated with FAS. They, too, exhibit a range of neurobehavioral problems reflecting some type of CNS damage, but typically, deficits are less severe, and a causal link to their prenatal alcohol exposure cannot be confirmed or ruled out. The documented array of disabilities in children with FASD likely contributes to social communication problems being one of the most prevalent characteristics of this population (Coggins, Olswang, Carmichael Olson, & Timler, 2003).

Social, Behavioral, Language, and Neuropsychological Characteristics of Children With FASD

Children with FASD who are enrolled in regular and special classrooms are frequently described as having difficulty managing social interactions, including notable behavior problems. Because prenatal exposure to alcohol can interfere with the developing brain at multiple levels and can alter the coordinated developmental schedule of the CNS, it can have long-term consequences for several domains of development that impact social performance and, ultimately, learning (Carmichael Olson, Morse, & Huffine, 1998; Streissguth & Kanter, 1997).

Data from teacher and parent questionnaires as well as anecdotal and clinical reports abound in reference to social and behavioral problems that these children exhibit (Brown et al., 1991; Carmichael Olson, Feldman, Streissguth, Sampson, & Bookstein, 1998; Coles et al., 1997; Kleinfeld & Wescott, 1993; Mattson & Riley, 2000; Steinhausen, Willms, Metzke, & Spohr, 2003; Streissguth & Kanter, 1997; Thomas, Kelly, Mattson, & Riley, 1998). The authors of these studies have used a variety of methodologies and terminology to describe performance; the focus in this review is on those characteristics that likely pertain to social communicative interactions. In research based on teacher and parent ratings of adaptive behavior, children with prenatal alcohol exposure are viewed as having difficulty managing social situations (e.g., Mattson & Riley, 2000; Steinhausen et al., 2003). For example, using the Vineland Adaptive Behavior Scales (Sparrow, Balla, & Cicchetti, 1984) to examine adaptive functioning of children with FASD as reported by their parents, Thomas et al. (1998) found that children diagnosed with the full FAS exhibited significant deficits across the three domains of communication, socialization, and daily living skills compared with typically developing children. Children with FAS were most impaired in the subdomain measuring interpersonal relationships. These researchers noted that the social problems associated with prenatal alcohol exposure did not appear to be solely the result of decreased cognitive functioning, suggesting that social abilities may be of particular concern (Thomas et al., 1998). Other researchers, using The Child Behavior Checklist (CBCL; Achenbach, 1991a, 1991b) to examine social skills and behavior problems as reported by parents or teachers, have found similar outcomes. Brown et al. (1991) discovered that children who had been exposed to alcohol throughout pregnancy were rated by

their teachers as showing more problem behaviors than children whose mothers never drank or stopped drinking by the second trimester. Likewise, using CBCL parent ratings, Mattson and Riley (2000) found that children with FASD were more impaired on the Total Problem scale than children who were not exposed to alcohol and who were matched for verbal IQ. Clinical observational reports also refer to social and behavioral problems as being commonly exhibited by children with FASD. For example, it has been reported that many children with FASD display impulsive, aggressive, assertive, and unpredictable behaviors (Aronson, 1997; Streissguth, 1997; Tanner-Halverson, 1997), and difficulty with peer interactions is a recurring theme (Kleinfeld & Wescott, 1993).

Researchers have noted that children with prenatal alcohol exposure have difficulty resolving conflicts and anticipating the consequences of their actions (Caldwell, 1993; Timler & Olswang, 2001; Timler, Olswang, & Coggins, 2005). Related specifically to the challenges that children with FASD face in interacting with peers, Timler and colleagues (Coggins et al., 2003; Timler, 2000) examined nine children with prenatal alcohol exposure using social conflict vignettes. The vignettes described a conflict with a peer that a child was asked to resolve. In comparison with typically developing peers, children with FASD produced fewer prosocial/engaged strategies for resolving conflicts and more passive/disengaged, hostile/coercive, assertive, and adult-seeking strategies. Even when the children were given choices for how they might resolve the conflicts, the children with FASD still selected fewer prosocial/engaged strategies and more hostile/coercive ones. These data are notable, suggesting that children prenatally exposed to alcohol would be at risk for problems in their social interactions.

In addition to social and behavioral problems being characteristic of this population, language difficulties have been repeatedly observed. Although language deficits have been hard to consistently document using standardized tests, problems using language in conversation and narratives appear prevalent (Coggins, Friet, & Morgan, 1998; Coggins et al., 2003; Thorne, Coggins, Carmichael Olson, & Astley, 2007). In particular, the challenges include difficulty producing language that takes into account the listener's perspective and responding appropriately to assumptions about shared knowledge. Recently, Thorne and colleagues (2007) found difficulties with the production of cohesive narratives by children with FASD resulting, in part, from errors with a syntactic element marking nominal reference. This error illustrates the link between syntax and language use, which is notable because it could disrupt communication during social interactions.

Further evidence on specific neuropsychological limitations exhibited by children with FASD may contribute to the challenges these children demonstrate during social interactions. Various studies have documented deficits in executive function, including limitations in planning, inhibition, self-regulation, attention, and memory (Coles et al., 1997; Kodituwakku, Handmaker, Cutler, Weathersby, & Handmaker, 1995; Mattson, Calarco, & Lang, 2006; Mattson, Goodman, Caine, Delis, & Riley, 1999). It appears that these deficits are manifested in performance decrements that are frequently accompanied by behavior problems and social ineptitude. Furthering the challenge for these children, Kodituwakku (2007) observed that the children's behavior suffers when task complexity increases—which, of course, is a hallmark of advancement in school and participation in academic and social situations.

Summary—Child Characteristics and the School Setting

In summary, the phenotype of children with FASD is characterized by social, behavioral, and language problems that disrupt interactions with peers and that appear to be influenced by task complexity. These characteristics—along with neuropsychological problems in planning, inhibition, self-regulation, and attention and memory—arguably contribute to the challenges facing these children in school settings. In particular, children with FASD may suffer in social and academic situations because their deficits interfere with their ability to be as engaged as they need to be. Student engagement, inferred from performance (attention, work completed, appropriate participation), is key to motivation and, ultimately, learning or mastering knowledge or skills (Newmann, Wehlage, & Lamborn, 1992). A number of researchers have shown the value of observation in addition to teacher report in identifying factors that might impact engaged performance in the classroom (Fredricks, Blumenfeld, & Paris, 2004; Powell, Burchinal, File, & Kontos, 2008). These studies, using an eco-behavioral approach, have begun to isolate factors (e.g., teacher talk, activity type) that can facilitate children's engaged performance. This approach has great appeal for examining the performance of children with FASD as they struggle with their deficits and strive to meet classroom expectations. However, prior to determining what factors might be influencing performance, first we need to (a) better understand and document the performance of children with FASD as they interact in classroom settings and (b) examine the differences between children with FASD and their typically developing peers. Determining the nature of performance in the classroom will not only reveal more about the phenotype but also provide implications as to how to better work with these children to improve social communication and, ultimately, school outcomes.

Social Communication—Observation

Social communication, which is viewed as ongoing verbal and nonverbal behaviors during interactive contexts, allows for the observation of behavioral states or dimensions as well as the observation of discrete, momentary behaviors. This approach has been advocated by several researchers interested in social interactions (Bakeman & Gottman, 1997) and classroom performance, particularly behavioral engagement (Fredricks et al., 2004). The value in viewing and coding states versus individual, momentary behaviors comes, in part, from research on peer relations, particularly in regard to peer acceptance and rejection. Specifically, Bierman (2004) argued that a child's social behaviors that are clustered into the dimensions of prosocial/cooperative, aggressive/disruptive, inattentive/immature, and anxious/avoidant provide the best empirical evidence that reflects peer social status and problematic peer relationships. These behavioral dimensions, or variations on these particular categories, have been used with different methodologies, such as peer nomination tasks or ratings (e.g., Pope, Bierman, & Mumma, 1991), teacher ratings (e.g., Flanagan, Bierman, & Kam, 2003), and observational rating scales (e.g., Ladd & Profilet, 1996). Recently, this dimensional view of performance was adopted for use in observational methodology designed to describe the frequency of occurrence of behavior states and their durations performed by children in classrooms (Olswang et al., 2006).

The Social Communication Coding System (SCCS; Olswang et al., 2006) was designed to capture how children spend their time as they interact with others in the classroom. Using a dimensional perspective based on the work by Bierman (2004) as well as by Asher and colleagues (e.g., Chung & Asher, 1996), a child's social communication status can be coded into one of six mutually exclusive categories suggesting manner of performance: prosocial/engaged, passive/disengaged, irrelevant, hostile/coercive, assertive, or adult seeking. For example, the dimension of *prosocial/engaged* is defined by verbal and nonverbal behaviors reflecting that a child is engaged in a task, such as a child's commenting, raising his or her hand, watching a demonstration, and/or asking a question. *Passive/disengaged* includes behaviors such as looking out the window or moving away from a group activity. The *irrelevant* dimension captures behaviors that are out of place, unrelated, extraneous, or odd according to what is expected at the time. The *hostile/coercive* dimension is defined by a child's verbal and nonverbal behaviors that reflect aggressive or intimidating actions, such as hitting, pushing, or teasing, versus the *assertive* dimension, which reflects a child's being firm or outspoken about an opinion but without crossing a line that is perceived as threatening. Finally, *adult seeking* refers to verbal and/or nonverbal communication that solicits help or attention from an adult. In the classroom, social communication as measured by dimensions is conceptualized as always occurring, with categories being mutually exclusive. As such, during a classroom activity, all categories of behavioral dimensions may occur, but research has indicated that these behavioral dimensions are not expected to be equally occurring. As identified by Powell and colleagues (2008), who recently examined engagement in early childhood classrooms, children spend their time primarily being engaged (47% of the time) or attentive (40% of the time).

An advantage of conceptualizing social communication behavioral dimensions is that performance may be analyzed as a function of occurrence as well as duration. Historically, frequency of occurrence has been useful in describing the individual behaviors that a child is demonstrating to illustrate his or her consistency or variety in performance during classroom interactions. For example, Damico (1992) counted frequency of illocutionary acts. Although informative, frequency of occurrence captures only part of the picture. Critical to the profile of children is the amount of time that they spend demonstrating each of the social communication behavioral dimensions; thus, duration becomes important to measure.

Two valuable types of duration data are the proportion of time and the average length of time that children spend demonstrating different social communication behavioral dimensions. *Proportion of time* reveals how much of a given time period (e.g., specific activity or part of a school day) a child spends demonstrating each social communication behavioral dimension (i.e., prosocial/engaged, passive/disengaged, irrelevant, hostile/coercive, assertive, adult seeking). *Average length of time* reveals the mean duration of each occurrence of a particular dimension. Across activities and/or days, an observer could create a profile of performance capturing how a child primarily performs. For example, a child who spends a relatively large proportion of an activity demonstrating irrelevant performance would likely be of concern, considering irrelevant behaviors are typically off task. Thus, for a thorough look at classroom performance, both frequency and duration measures are critical.

Purpose of the Research

The increasing difficulties that children with FASD exhibit in social situations as they grow older no doubt result from greater societal demands to be responsive to a variety of individuals across a variety of situations. Managing social interactions becomes increasingly

important and challenging when children enter school (Campbell & Siperstein, 1994). To date, research has not documented real-time social communication performance for this population in natural settings, such as school, to validate teacher and parent concerns. The overall sense is that social/behavioral problems exist, but the nature and extent of these problems as they are manifested in everyday settings during social communication interactions are not well understood. Specifically, research has not quantitatively documented the classroom performance of children with FASD, particularly those on the mild end of the continuum who are enrolled in regular education classrooms.

The purpose of this research was to examine the social communication performance of children with FASD compared with their matched, typically developing peers during classroom activities. In the study, we used an observational methodology that employed a behavioral dimensional coding taxonomy yielding frequency and duration data. The following general question was addressed: When social communication performance is divided into six mutually exclusive dimensions (prosocial/engaged, passive/disengaged, irrelevant, hostile/coercive, assertive, and adult seeking), do two groups of children (i.e., a group diagnosed with FASD and a group of matched, typically developing peers) demonstrate different profiles of social communication in regard to frequency of occurrence and duration (proportion and average length of time) of each dimension in a classroom setting?

Method

Participants

In this paired, case-control study, participants consisted of 12 children with FASD (cases) and 12 typically developing (TD) children (controls), ages 7;5–11;8 (years;months). Each child with FASD was pair matched on gender and age to a TD classmate in the same regular education classroom; therefore, this study included 12 classrooms. Each matched pair was observed alternately in their classroom to document social communication performance using the SCCS (Olswang et al., 2006), a behavioral dimensional coding system. The children with FASD were previously diagnosed and recruited through the Washington State Fetal Alcohol Syndrome Diagnostic and Prevention Network (FAS DPN) at the University of Washington (described in the sections that follow). The TD children were identified by their respective teachers. For all children, consent to enroll was obtained from the caregiver, the child's teacher, and the child (i.e., informed assent) following the University of Washington Human Subjects Institutional Review Board approval policy. Demographic data were obtained from the caregiver.

Identification and Selection of FASD Participants

For this study, we recruited children with FASD who met the inclusion/exclusion criteria detailed in the subsections that follow.

Inclusion Criteria

Each child had to meet six criteria for inclusion in the study:

1. Child was age 7;0–12;0.
2. Child had an FASD diagnosis of FAS, partial FAS, static encephalopathy/alcohol exposed, or neurobehavioral disorder/alcohol exposed. The last two diagnoses are comparable to the U.S. Institute of Medicine (Stratton et al., 1996) diagnostic criteria for ARND with confirmed prenatal alcohol exposure. More specifically, they would be equivalent to severe and mild ARND, respectively.
3. Child performance was in the clinical range on the Problem Behaviors subscale (i.e., standard score > 115) of the Social Skills Rating System (SSRS)–Teacher Form (Gresham & Elliott, 1990). Sample items from the Problem Behaviors component of the SSRS include fights with others, threatens or bullies others, appears lonely, appears easily distracted, interrupts conversations, disturbs others, does not listen to what others say, has temper tantrums, and acts impulsively. We included this criterion to further ensure that the children identified by the FAS DPN met the description of the FASD phenotype as described previously.
4. Child had a composite IQ score of no more than 1.0 *SD* below the mean (i.e., a standard score $\geq$ 85) on the Kaufman Brief Intelligence Test (Kaufman & Kaufman, 1990; administered by a certified speech-language pathologist [SLP]).
5. Child had been mainstreamed in a regular education classroom.
6. Child was residing in the greater Seattle area.

Exclusion Criteria

Children were excluded if they met any of the following five criteria:

1. Eligible comparison classroom peer could not be identified.
2. There was a confirmed presence of severe psychiatric condition (e.g., schizophrenia, pervasive developmental disorder, etc.).
3. There was a confirmed presence of severe physical or motor handicaps.

4. Child had hearing or vision impairment.
5. English was not used as primary language at home.

Identification and Selection of TD Participants

The TD control participants were identified by the regular education teacher in the classroom of the experimental participant with FASD. For this study, we recruited TD control participants who met the inclusion/exclusion criteria detailed in the subsections that follow.

Inclusion Criteria

Children had to meet the following five criteria for inclusion in the study:

1. Child was enrolled in the same classroom as the pair-matched child with FASD. The teacher was asked to select a child who was as close a cognitive match as possible.
2. Child performance was not in the clinical range on the Problem Behaviors subscale (i.e., standard score < 115) of the SSRS–Teacher Form (Gresham & Elliott, 1990).
3. Child had a composite IQ score of no more than 1.0 *SD* below the mean (i.e., a standard score $\geq$ 85) on the Kaufman Brief Intelligence Test (Kaufman & Kaufman, 1990).
4. Child was the same gender as the child with FASD to whom he or she was matched.
5. Child's chronological age was within ±6 months of the chronological age of the matched child with FASD.

Exclusion Criteria

Children were excluded if they met any of the following four criteria:

1. There was a confirmed presence of severe psychiatric condition (e.g., schizophrenia, pervasive developmental disorder, etc.).
2. There was a confirmed presence of severe physical or motor handicaps.
3. Child had hearing or vision impairment.
4. English was not used as primary language at home.

Table 1 presents the sociodemographic and clinical description of the study population. The FASD group consisted of one child with partial FAS, two with severe ARND, and nine with mild ARND. The FASD–control pairs were effectively matched on age and gender. IQ was also comparable between the two groups. By design, the FASD group had a significantly higher mean score on the Problem Behaviors subtest of the SSRS.

Equipment

Data on social communication behavior dimensions and type of situation in which they occurred were collected in real time in the classroom using the SCCS (Olswang et al., 2006), which is a handheld computer–based (Palm, M100) coding system developed by the Child Language Laboratory at the Department of Speech and Hearing Sciences, University of Washington. The sessions were not videotaped. This technology allowed for coding the duration of social communication behavioral dimensions. Specifically, as the researcher observed the child in the school environment, data were entered by tapping a stylus on specific entries via drop-down menus.

Selecting a child social communication behavioral dimension started a time code for that dimension. On selecting a new dimension, the duration of the previous dimension ended, and the duration for the new code started. The dimensions were mutually exclusive, and only one could be selected at a time. As long as the observation was occurring, a code was entered into the Palm device. The data were coded by subject number and observer number and were later sent to a secure central database for analysis (American Head and Neck Society Speech and Language Otobase; Coltrera, 2002).

SCCS: Behavioral Dimensions

The SCCS included six *behavioral dimensions*—that is, clusters of discrete behaviors to describe state or manner of performance (based on Bierman, 2004; Chung & Asher, 1996)—which are described in the text that follows.

Prosocial/engaged. This dimension reflected a child being engaged in a social interaction or the school activity relative to teacher's expectations, school rules, or the surrounding context (e.g., peer behaviors). Examples include listening attentively, on-task work or conversations, helping, sharing, compromising, and making an appropriate request or comment. For instance, during a cooperative group work activity, a child may constructively interact with his or her peers using appropriate language and staying on task, thus displaying prosocial/engaged behavior.

Passive/disengaged. This dimension reflected a child's lack of involvement in the situation or activity and/or physical disengagement from the activity. Examples include staring into space, putting his or her head down, or walking away from an activity without a clear

Table 1. Clinical and sociodemographic description of the study population: Children with fetal alcohol spectrum disorders (FASD) and their typically developing (TD) matched peers.

Characteristic	FASD (*n* = 12)	TD (*n* = 12)	Stat	*p*
Age in years: *M (SD)*	9.2 (1.1)	9.1 (1.3)	paired $t = 0.32$	.75
Gender—Females: *n* (%)	6 (50)	6 (50)	χ^2 Yates = 0.17	.68
Race—Caucasian: *n* (%)	6 (50)	4 (33)	χ^2 Yates = 0.67	.41
SSRS Problem Behavior Standard Score: *M (SD)*	122.8 (7.4)	92.5 (9.0)	paired $t = 10.23$	.000
K-BIT IQ Standard Score: *M (SD)*	109.8 (12.5)	114.7 (10.8)	paired $t = -1.36$	.20
FASD 4-digit code diagnosis: *n*			N/A	
Full FAS	0	0		
Partial FAS	1	0		
Static encephalopathy/alcohol exposed[a]	2	0		
Neurobehavioral disorder/alcohol exposed[b]	9	0		
Typical development/no alcohol exposure	0	12		
Grade level: *n* (%)			$\chi^2 = 0.0$	1.0
Grade 2	5 (42)	5 (42)		
Grade 3	2 (17)	2 (17)		
Grade 4	4 (33)	4 (33)		
Grade 5	1 (8)	1 (8)		
Home placement: *n* (%)			$\chi^2 = 12.6$	.000[c]
Birth family	1 (8)	10 (82)		
Adoptive family	8 (67)	1 (8)		
Foster family	3 (25)	0 (0)		

Note. SSRS = Social Skills Rating System–Teacher Form (Gresham & Elliott, 1990); K-BIT = Kaufman Brief Intelligence Test (Kaufman & Kaufman, 1990); Stat = statistic; N/A = not applicable. Blank cells indicate xxxxxxxxxxxxxxxxxxxx.

[a]Equivalent to Institute of Medicine (IOM) severe alcohol-related neurodevelopmental disorder (ARND). [b]Equivalent to IOM mild ARND. [c]Birth family versus other placement.

purpose or instruction. For instance, when working together with peers on solving a problem, a child may become passive/disengaged and put his or her head down instead of actively participating in the ongoing discussion.

Irrelevant. This dimension reflected (a) a child being actively engaged in an off-task behavior in which the child says or does something that he or she is not supposed to do according to teacher instructions and classroom rules or (b) behaviors that are out of place, unrelated, extraneous, or odd. Examples include starting an activity that is different from the teacher-directed task, fiddling with objects as a main focus of attention, engaging in goofy or silly behaviors, or saying something that bears no relationship to the task at hand. For instance, during a class discussion, a child may engage in irrelevant behavior by leaning back and whispering to a peer.

Hostile/coercive. This dimension reflected a child's aggressive behavior or ridicule of another child; typically, these behaviors would be considered unacceptable in a social situation, according to the teacher and the rules of the school. Examples include grabbing, hitting, pinching, kicking, pushing, taunting, provoking, yelling, and screaming. For instance, during negotiating a conflict with peers, a child might get hostile and hit or scream.

Assertive. This dimension reflected a child stating a position, opinion, or idea in a firm, persistent, or bold way. Examples include stressing a point, demonstrating an assertion of rights or beliefs (verbally or nonverbally), and persuading or directing another person. For instance, when a peer leans over and whispers something during quiet independent work, a child may firmly state, "Stop whispering! I have to finish this," thus displaying assertive behavior.

Adult seeking. This dimension reflected a child making an effort to seek assistance or attention from an adult. Examples include requesting help from an adult, summoning the teacher from across the room, and moving to the teacher to initiate an interaction. For instance, during a small-group discussion, a child goes to find the teacher and asks the teacher if he or she will tell the child's peers that they need to listen to the child's ideas.

Classroom Setting and Specific Data Collection Procedures

Within 2 weeks of qualifying for entry into the study, data on the children's social communication performance were collected in the children's classroom. Observations

were conducted 20 min per day for each child, on 4 separate days, occurring within 2 weeks whenever possible. The time period of 4 days was selected for three major reasons: (a) representativeness—recommendations that observational data be collected for at least two or three sessions in the setting of concern (following Walker, Ramsey, & Gresham, 2004); (b) feasibility—challenges associated with arranging and scheduling observations in the schools; and (c) maturation effects—intent of capturing performance within a short enough period of time to avoid child maturation/development or changes that might occur in the classroom over time. Each observation was conducted in the respective classrooms of each child pair. Children were observed in their classrooms at times that were convenient to the teacher. However, the teachers made an effort—at the request of the study team—to include two major types of activities: (a) small-group, cooperative work among students and (b) large-group work involving the teacher as leader. The former included math, science, and art activities, in which the students worked in small groups to complete a specific task. The latter involved the teacher at the "head of the class" giving instructions, leading a discussion, or giving a test. Because the intent of this study was to observe children in their natural environment, requests to the teacher to alter his or her typical day were held to a minimum. To account for day and activity effect, data were collected for the TD-matched peer on the same days as for the child with FASD. The coder alternated between observing the child with FASD and his or her matched peer in 5-min sessions (20 min per child) as they participated in classroom activities. Order of coding was counterbalanced by alternating which child was coded first on the different observation days. The coder observed for 5 min before starting the actual coding in order to reduce subject reactivity. The child was allowed to interact with any peer(s) or with the teacher during the observations. The goal was to be an unobtrusive observer.

Observational data were collected by three trained observers. Observer training is described in the section that follows. All observers were female certified SLPs with an average of 12.3 years of clinical experience (3, 5, and 29 years, respectively). These observers were different from the SLP who conducted initial testing. Because the informed assent was obtained from the children at the time of initial testing, the children were aware of the observers' participation in a study but had not met the observers.

Before the observations started, the observer(s) spent a few minutes talking to the teacher to get further information about the classroom (e.g., activity), how the experimental and control children were doing that day, best positions for observing, restrictions about walking around the room, and reminding the teacher about how to introduce the observers. The teacher subsequently introduced the observer(s) by telling the class: "We have one (two) visitors from the University of Washington who will be watching our class today. They will be staying a while today and other days. They will be sitting or walking around quietly taking some notes."

Observers arranged themselves as close to the target child as possible in order to hear conversations and see the target child's gestures and nonverbal cues from a front or side angle view. Often, this entailed some quiet moving around the classroom, especially during small-group activities. In order to be as unobtrusive as possible, observers looked at a variety of children in the classroom or the teacher during the first 5 mins before actual coding started and during intermissions between coding sessions.

Observer Training

Training of the three observers occurred over 3 months for approximately 30 hr (see Olswang et al., 2006, for details). Training involved a series of phases including discussing relevant articles addressing social communication; reading the *SCCS Procedural Manual* (Olswang & Svensson, 2005), which included definitions of behavioral dimensions, examples, and short written quizzes; and then practicing and being tested on coding of children in a variety of classroom settings via videotape. Video coding was done independently by observers and then was compared using the Kappa (κ) coefficient. Live coding was not allowed until interobserver agreement testing achieved a κ value of .60 or better on at least one set of ten 2-min video segments. Guidelines for interpreting κ values were borrowed from Cicchetti and Sparrow (1981).

Observer Agreement for In-Class Observation

To examine interobserver agreement during the live observations, approximately 25% of the data were coded concurrently by two independent observers. Eighteen children were observed simultaneously by two observers (nine children with FASD and nine TD children) for 1 or 2 days. Following Olswang and colleagues (2006), interobserver agreement was assessed using time-interval analysis. This procedure—which was based on the work of Cordes, Ingham, Frank, and Ingham (1992)—divides an observation period into fixed time-interval units, which allows for comparison across observers. Time-interval analysis is an effective and appropriate strategy that can be applied to analyzing agreement of occurrence and duration judgments (Cordes et al., 1992; Olswang et al., 2006). Agreement is determined by dividing the actual time frame of observation into fixed time-interval units for comparison across observers. Breaking down the entries into preset intervals allows for an interval-by-interval comparison of type of behavior present; the continuous,

real-time duration data may now be manipulated and analyzed for agreement in the same way as data collected using interval recording. In the present research, time-interval units for examining reliability were set to 5 s because this is the shortest duration in which any coding entry can be conducted and based on the results by Olswang and colleagues (2006). For each interval, the dimension that was coded defines the interval. If two behaviors occur during the interval, the one with the longest duration defines the interval. Using the interval data, Cohen's κ was calculated to provide a summary agreement score between observers for coding the six SCCS behavioral dimensions for each child whose data were included in this analysis. In addition, to provide another index of agreement, point-by-point percent agreement between intervals was calculated using the same data set for each child. Table 2 provides a list of children with number of observation days, number of 5-min observation sessions, and number of intervals included in agreement analyses. This table also presents the κ values and point-by-point percent agreement for the independent observers' coding of the agreement data set for each child using an interval-by-interval analysis. Guidelines for "acceptable" κ values followed the recommendations of Cicchetti and Sparrow (1981): κ < .40 = poor agreement; κ between .40 and .59 = fair agreement; κ between .60 and .74 = good agreement; κ > .75 = excellent agreement. For percent agreement, an "acceptable" agreement level was defined as at least 80% agreement (following Cordes et al., 1992). Using these guidelines, the data of five children stood out as below the acceptable level of agreement either by virtue of their overall κ value or point-by-point percent agreement. For these children, point-by-point percent agreement, including chance, was calculated for all codes that the children demonstrated. These data are presented in Table 3. The results presented in this table indicate high point-to-point agreement for each of the behavioral dimensions. In all cases, percent agreement is equal to (i.e., TD11: passive/disengaged) or better than chance when the behavioral dimension occurred. It is worth noting the high levels of chance; this reflects, for some categories, extremely high levels of occurrence or nonoccurrence of entries, which is known to increase chance (McReynolds & Kearns, 1983). This is particularly noteworthy for the categories of hostile/coercive, assertive, and adult seeking. These data indicate that the agreement analyses, which were conducted live in the school setting, were comparable to the agreement that was achieved via videotapes (Olswang et al., 2006), confirming the success of the training and SCCS coding.

Data Reduction

Children's social communication performances in classrooms were coded into the six mutually exclusive social communication behavioral dimensions via the SCCS, as described previously. These coded data were

Table 2. Live observation (Social Communication Coding System) interobserver agreement using time-interval analysis: Overall κ (all codes) and point-by-point percent agreement between coded intervals.

Participant	Days	Number of 5-min observation sessions	Number of total 5-s intervals	κ	% point-by-point agreement between coded intervals
FASD1	2	6	382	.69	82
TD1	2	8	510	.49[a]	96
FASD2	1	5	321	.66	95
TD2	1	4	254	.85	99
FASD4	2	8	510	.67	87
TD4	2	8	504	.29[a]	89
FASD5	2	8	509	.62	87
TD5	2	7	401	.56[a]	85
FASD8	1	4	257	.74	83
TD8	1	4	255	.67	87
FASD9	1	5	318	.69	89
TD9	1	4	250	.65	97
FASD10	1	3	191	.84	95
TD10	1	3	193	.90	98
FASD11	1	5	254	.66	84
TD11	1	4	249	.48[a]	92
FASD12	1	4	236	.58[a]	78[a]
TD12	1	4	254	.70	90

[a]For overall κ < .60 and/or percent agreement < 80%, point-by-point agreement—including chance—was calculated for each of the social behavioral dimensions (see Table 3).

Table 3. Point-by-point agreement (and chance) for all behavioral dimensions.

		% point-by-point agreement (and chance)						
Participant	κ all codes	All codes	Prosocial/engaged	Passive/disengaged	Irrelevant	Hostile/coercive	Assertive	Adult seeking
TD 1	.49	96	96 (92)	99 (98)	97 (94)	99 (99)	99 (99)	No occurrence
TD 4	.29	89	91 (86)	97 (94)	94 (93)	99 (99)	98 (98)	No occurrence
TD 5	.56	85	90 (68)	91 (86)	93 (82)	99 (99)	99 (99)	97 (97)
TD 11	.48	92	93 (85)	97 (97)	94 (87)	No occurrence	No occurrence	No occurrence
FASD 12	.58	78	86 (57)	93 (87)	85 (68)	No occurrence	No occurrence	97 (93)

used for data reduction and analysis. As a reminder, actual coded data, not interval data, were used for data reduction and analysis; intervals were used only for examining interobserver agreement. Coded data were summed across the four observation days to ensure representativeness of child performance (note that day-to-day performance variation was examined in a separate study; see Svensson, 2006). Four primary outcome measures were computed to document the performance based on the six social communication behavioral dimensions, as follows: (1) number of children exhibiting each of the behavioral dimensions, (2) frequency of occurrence of each behavioral dimension that was coded, (3) proportion of time spent in each coded dimension, and (4) average length of time (in seconds) spent in each coded dimension. Number of children exhibiting each type of social communication behavioral dimension was used descriptively to compare the groups of children based on the array of behaviors that they demonstrated. Frequency of occurrence indicated the total number of times that each behavioral dimension was coded for each child. *Proportion of time* was defined as the total duration (in seconds) of a behavioral dimension totaled across the 4 observation days divided by the total duration of the observation (typically 80 min; i.e., 20 min per observation day) multiplied by 100. *Average length of dimension occurrences* was defined as the total duration of a behavioral dimension (in seconds) divided by the total number of occurrences of that dimension totaled across the 4 observation days.

Data Analysis

Differences with regards to frequency, proportion of time, and average length of time spent in each behavioral dimension were compared between the FASD and TD groups using the paired t test. The number of children presenting each behavioral domain was compared between the FASD and TD groups using the χ^2 or the Fisher exact test. Effect sizes were examined using Glass's d (Glass, McGaw, & Smith, 1981), a standardized mean difference derived by dividing the difference between the FASD group's mean and the TD group's mean by the *SD* of the TD group's scores. A d of ≥ 0.80 has been suggested as reflecting a large effect size—that is, a large magnitude of an effect/difference (Cohen, 1988).

Results

Table 4 presents the results for all aspects of the data analysis. First, to examine diversity of performance using the SCCS, we examined the data to determine the number of children exhibiting each of the behavioral dimensions. Most children in both groups presented at least one occurrence of prosocial/engaged, passive/disengaged, irrelevant, and adult-seeking behavior (see Table 4). No more than half the children in each group presented with any hostile/coercive behavior. The number of children presenting one or more occurrence of each behavioral domain was comparable between the two groups.

In the second part of the analysis, we examined frequency of occurrence of each behavioral dimension that was coded. As displayed in Figure 1, children in the FASD group, on average, exhibited more occurrences of each behavioral dimension than children in the TD group: prosocial/engaged (FASD = 50.0 occurrences, TD = 39.0 occurrences); irrelevant (FASD = 27.8 occurrences, TD = 14.9 occurrences); passive/disengaged (FASD = 14.8 occurrences, TD = 6.3 occurrences); adult seeking (FASD = 3.3 occurrences, TD = 2.8 occurrences); assertive (FASD = 4.1 occurrences, TD = 3.3 occurrences); and hostile/coercive (FASD = 1.1 occurrences, TD = 0.4 occurrences). Frequency of occurrence was significantly different between the groups for the following dimensions: prosocial/engaged, $t(11) = 6.1, p < .001, d = 1.9$; irrelevant, $t(11) = 4.9, p = .001, d = 1.9$; and passive/disengaged, $t(11) = 8.1, p < .001, d = 3.2$. Although children in the FASD group were more likely to exhibit more occurrences of adult-seeking, assertive, and hostile/coercive performances relative to the children in the TD group, these differences were not statistically significant (see Table 4).

In regard to proportion of time spent in each coded dimension, the observations revealed that both groups spent the majority of their time (over 76%) in prosocial/engaged behavior (see Figure 2). Moreover, on average, children in both groups spent most of their time

Table 4. Comparison of the frequency, proportion, and average length of time for each behavioral dimension between the FASD and TD groups across all 4 observation days.

Behavioral dimension	FASD (*n* = 12) *M (SD)*	TD (*n* = 12) *M (SD)*	Statistic	*p*
Prosocial/engaged				
Number of children with 1 or more occurrences of the domain	12	12	0.0[b]	1.0
Frequency of occurrence	50.0 (7.4)	39.0 (5.9)	6.1[a]	.000
Proportion of time	76.7 (9.7)	89.3 (5.4)	–4.6[a]	.001
Average length of time (in s)	88.6 (18.1)	127.5 (26.9)	–7.2[a]	.000
Irrelevant				
Number of children with 1 or more occurrences of the domain	12	12	0.0[b]	1.0
Frequency of occurrence	27.8 (11.6)	14.9 (6.7)	4.9[a]	.001
Proportion of time	15.8 (8.1)	7.2 (4.9)	4.3[a]	.001
Average length of time (in s)	32.3 (12)	25.0 (9.3)	2.3[a]	.044
Passive/disengaged				
Number of children with 1 or more occurrences of the domain	12	12	0.0[b]	1.0
Frequency of occurrence	14.8 (3.6)	6.3(2.7)	8.1[a]	.000
Proportion of time	5.4 (2.4)	1.8 (1.1)	4.4[a]	.001
Average length of time (in s)	20.8 (8.3)	14.7 (5.6)	2.3[a]	.044
Adult seeking				
Number of children with 1 or more occurrences of the domain	12	10	0.0[c]	0.47
Frequency of occurrence	3.3 (3.0)	2.8 (2.5)	0.6[a]	.591
Proportion of time	1.1 (1.1)[d]	1.0 (1.3)	0.1[a]	.915
Average length of time (in s)	14.4 (8.0)	14.5 (13.1)	–0.03[a]	.973
Assertive				
Number of children with 1 or more occurrences of the domain	9	8	0.0[c]	0.0
Frequency of occurrence	4.1 (3.7)	3.3 (4.0)	0.8[a]	.453
Proportion of time	0.8 (0.7)	0.5 (0.7)	1.5[a]	.163
Average length of time (in s)	10.9 (11)	5.7 (4.7)	1.7[a]	.111
Hostile/coercive				
Number of children with 1 or more occurrences of the domain	6	4	0.2[b]	0.68
Frequency of occurrence	1.1 (1.2)	0.4 (0.7)	1.5[a]	.151
Proportion of time	0.3 (0.4)	0.1 (0.2)	1.4[a]	.194
Average length of time (in s)	6.0 (7.8)	3.4 (5.7)	0.9[a]	.399

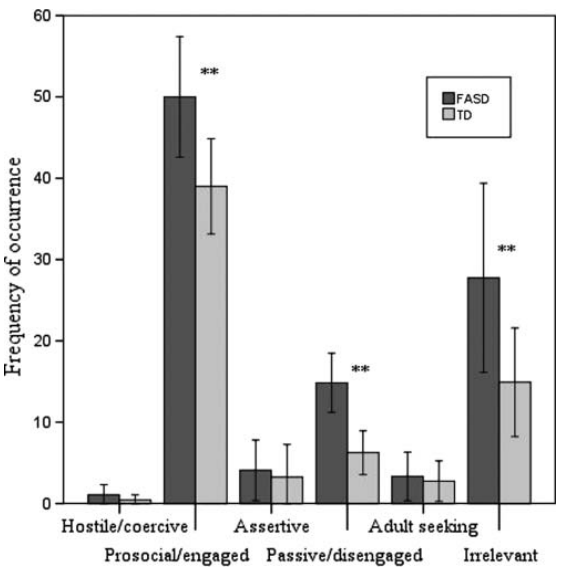
Note. s = seconds.

[a]statistic = paired *t* test. [b]statistic = chi-square. [c]statistic = Fisher exact test. [d]The .1 difference in values between Table 4 and Figure 2 reflect a rounding artifact.

exhibiting three of the dimensions: prosocial/engaged (FASD = 76.7%, TD = 89.3%); irrelevant (FASD = 15.8%, TD = 7.2%); and passive/disengaged (FASD = 5.4%, TD = 1.8%). Results of the paired *t* tests confirmed the pattern seen in the descriptive data for these three major dimension categories. Children with FASD spent significantly less time demonstrating prosocial/engaged performance than did TD children, $t(11) = -4.6$, $p = .001$, $d = -2.3$. In contrast, children with FASD spent significantly more time than their matched peers in irrelevant, $t(11) = 4.3$, $p = .001$, $d = 1.7$, and passive/disengaged, $t(11) = 4.4$, $p = .001$, $d = 3.2$, performances. Although children with FASD spent more time demonstrating adult-seeking, assertive, and hostile/coercive behaviors relative to the children in the TD group, these differences were slight and not statistically significant (see Table 4).

Finally, when examining average length of time (in seconds) spent in each coded dimension, Figure 3 shows

Figure 1. Mean frequency of occurrence of the Social Communication Coding System behavioral dimensions for children with fetal alcohol spectrum disorders (FASD) and typically developing (TD) children. Error bars denote ± 1 *SD*. Group differences were examined using the paired *t* test. $^{**}p < .01$.



that instances of the three dimension types in which the children spent most of their time, on average, also were the longest: prosocial/engaged (FASD = 88.6 s, TD = 127.5 s); irrelevant (FASD = 32.3 s, TD = 25.0 s); and passive/disengaged (FASD = 20.8 s, TD = 14.7 s). Results revealed that instances of prosocial/engaged behavior were significantly shorter for children with FASD when compared with instances of coded prosocial/engaged behavior exhibited by children in the TD group, $t(11) = -7.2$, $p < .001$, $d = -1.4$. On the contrary, instances of irrelevant behavior were significantly longer for the children with FASD than for TD peers, $t(11) = 2.3$, $p = .044$, $d = 0.8$. This pattern was observed for passive/disengaged performances as well, $t(11) = 2.3$, $p = .044$, $d = 1.1$. Although not significant, the average length of time for occurrences of assertive and hostile/coercive behavior was longer for children with FASD than for TD matched peers (see Table 4). Average length of time for adult-seeking occurrences was comparable across the two groups of children.

Discussion

Summary of Findings

Data revealed that children with FASD and TD children display a similar array of behavioral dimensions

Figure 2. Mean proportion of time spent in the Social Communication Coding System behavioral dimensions by children with FASD and TD children.

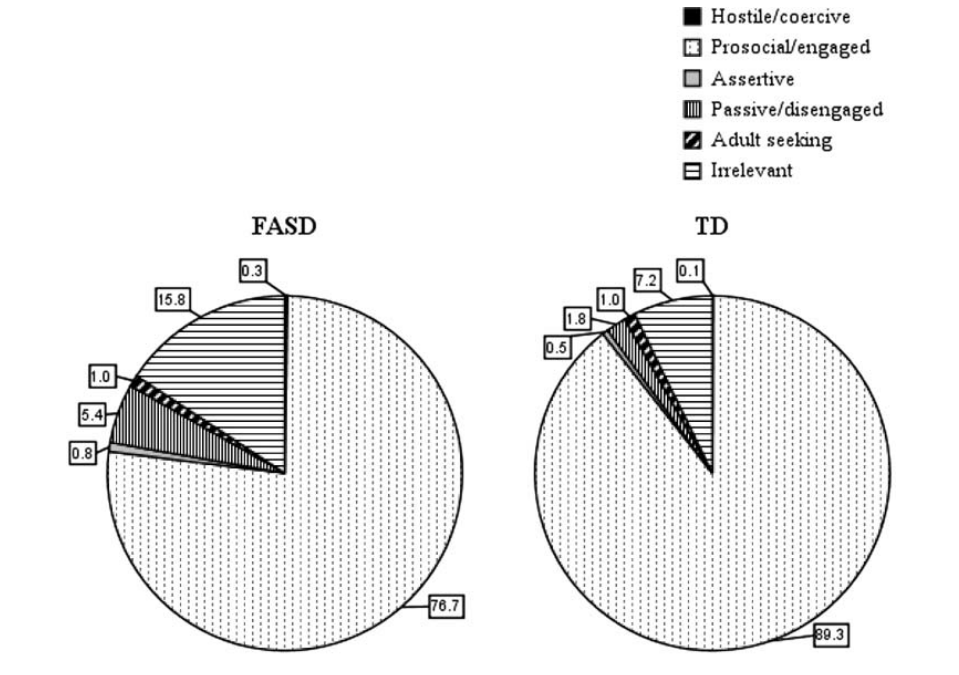
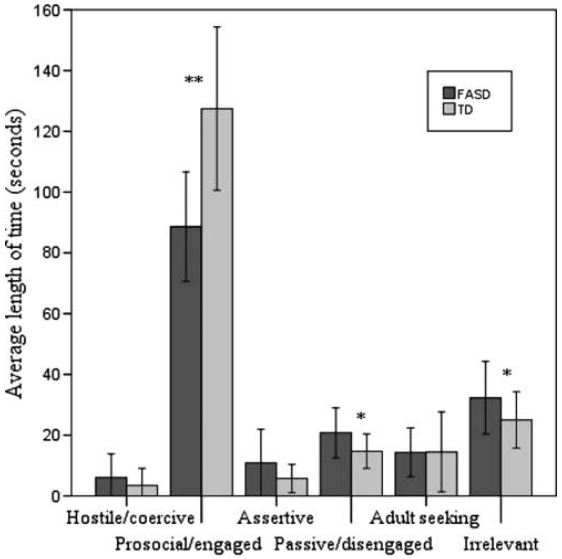


Figure 3. Mean average length of time of Social Communication Coding System behavioral dimension instances for children with FASD and TD children. Group differences were examined using the paired *t* test. $*p < .05$. $**p < .01$.



during classroom activities. During the course of a 4-day observation, both groups of children demonstrated performances that could be categorized into the six social communication behavioral dimensions. The predominant performances in terms of proportion of time displayed in the classroom were prosocial/engaged, irrelevant, and passive/disengaged, with both groups of children spending most of their time demonstrating prosocial/engaged performances. The predominance of prosocial/engaged performance corresponds to the results reported by Powell and colleagues (2008). Compared with their matched TD peers, children with FASD spent a smaller proportion of their time displaying prosocial/engaged performance and a larger proportion of their time displaying passive/disengaged and irrelevant performances. With regard to the average length of occurrences of the predominant dimensions, the results revealed that for children with FASD, prosocial/engaged occurrences were shorter than those of their matched peers, and passive/disengaged and irrelevant occurrences were longer than those of their matched peers. Taken together, the frequency and duration data suggest that children with FASD have more occurrences of prosocial/engaged behavior than do their TD peers; however, overall, the proportion of time that they spend being prosocial/engaged is smaller, and the average length of each such instance is shorter than that of their TD peers. Further, they have more passive/disengaged and irrelevant occurrences than do their TD peers, and the proportion and average length of time in these off-task behaviors are larger and longer, respectively, than those of their peers. The previously discussed differences between the groups concerning frequency, proportion of time, and average length of time with regard to the prosocial/engaged, irrelevant, and passive/disengaged dimensions are not only statistically significant but also important in magnitude, as reflected by large effect sizes. Hence, they are likely to be clinically relevant.

This study was designed to explore the social communication performance of children with FASD as they participated in their classrooms as a way to further understand the nature of their problems. We accomplished this objective by examining the differences in social communication profiles between children with FASD and their matched peers in the classrooms. The research successfully revealed new information about the nature of social communication problems that characterize children with prenatal alcohol exposure, particularly those who are on the mild end of the continuum and who are enrolled in regular education classrooms. Further, surprising similarities—as well as differences—emerged as the two groups were compared.

Classroom Performance From a Dimension Perspective: Children With FASD and TD Children

The observational data from this research indicate that children diagnosed with FASD and their TD matched peers spent most of their time demonstrating prosocial/engaged behaviors, followed by irrelevant and passive/disengaged performances. This is a significant finding, particularly for the sample of children with FASD. These data reveal that in general, children with mild FASD perform similarly to their peers in the classroom during both small-group and large-group activities with regard to behavior states/dimensions. Perhaps the message is "children are children" and that school performance of children between the ages of 7 and 12 involve both on-task and off-task performance throughout the day—and even children who are identified as having problem behaviors do not exhibit large extremes in their performance. Both groups spent most of their time being prosocial/engaged—well over 70% of the time across all days and classroom activities—as was expected. Yet, all of the children spent some proportion of their time exhibiting irrelevant and passive/disengaged performances. Until now, this degree of similarity has not been documented. This finding seems particularly revealing in light of the extensive literature describing the social/behavioral problems of children with FASD.

The observational data enlighten our understanding of the nature of the problems that have been noted in the FASD population. Findings from this study validate other literature indicating that children with FASD are characterized by problems interacting with others, yet this study reveals important nuances. Notably, the children with FASD did not demonstrate a significant number of hostile/coercive or assertive behaviors during the observation period, as might have been expected given the literature cited earlier, particularly Aronson (1997), Streissguth (1997), Tanner-Halverson (1997), and Timler (2000). Perhaps this finding reflects the influence of a relatively structured classroom environment on the children's performances. As shown in a case study of a school-age boy with FAS, Timler and Olswang (2001) explained that the boy's behavioral and social performance varied between the school and home environment, seemingly as a result of the difference in structure between the two settings. Another possibility for the limited occurrence of hostile/coercive and assertive behaviors is that the children with FASD in this study were on the mild end of the continuum and were enrolled in regular education classrooms. The research cited earlier in regard to hostile, assertive, and aggressive behavior included children across the FASD continuum. The results from our research suggest that "standout" hostile/coercive or assertive performance as defined by the SCCS protocol may not be accounting for the problem-behavior status of the children with FASD as noted by teachers. In fact, as noted earlier, items from the Problem Behaviors component of the SSRS involves a range of behaviors, including "is easily distracted," "interrupts conversations of others," "acts impulsively," and "disturbs ongoing activities," along with more aggressive and assertive behaviors such as "fights with others" and "threatens or bullies others" (Gresham & Elliot, 1990). High ratings by teachers (i.e., the behavior occurs very often) on the former (less aggressive and assertive) type of items could result in categorizing a child as having problem behaviors according to the SSRS rather than high ratings for the latter (more aggressive and assertive) items.

The results from this observational study serve to enlighten our understanding of why children on the mild end of the FASD continuum may be described as exhibiting problem behaviors. Recall that during the observation period, the children with FASD demonstrated predominantly prosocial/engaged behavior during classroom activities; in fact, frequency of occurrence for this coded dimension was larger for the children with FASD than for their typical peers. However, the proportion of time and average length of each occurrence were shorter than those demonstrated by TD children. These data suggest that children with FASD—particularly on the mild end of the continuum—may have problems sustaining attention, and this, in turn, may lead to their increased challenges in learning and behaving appropriately in class rather than to extremes in behavior (such as those viewed as hostile/coercive or assertive).

Contributing to the profile of children with FASD in this study are the behaviors exhibited that were coded as irrelevant and passive/disengaged. All children act irrelevant or disengage during the school day, but what seems to be true for the children with FASD is that they did so more often (frequency of occurrence data) and for a greater proportion of the day than their peers. Further, when the children with FASD were irrelevant or passive during the observations, these "bouts" lasted longer than the "bouts" of their peers. These factors—in combination with the shorter periods of prosocial/engaged performance—seemingly could account for why these children are notable to their teachers as exhibiting "behavior problems" and why these children are less successful in school. This study revealed that although in large part, children at the mild end of the continuum for FASD act like their peers in the classroom from a social communication behavioral dimensional perspective, they are, in fact, different in regard to being engaged versus disengaged. Their documented performance differences are ones that could call attention to themselves and, perhaps, even be disruptive—or at least counterproductive—in the classroom. These results suggest that the differences noted between groups in the performance of prosocial/engaged, irrelevant, and passive/disengaged dimensions could be accounting for at least part of the problem-behavior status of the children with FASD rather than more conspicuous behaviors, such as those categorized as hostile/coercive or assertive.

The children included in the experimental group in this research were selected because of their prenatal alcohol exposure and behavior problems to confirm the characteristics of the phenotype for FASD. These inclusionary criteria did not allow us to argue convincingly that prenatal alcohol exposure was solely responsible for differences between groups. Nevertheless, the data granted us the opportunity to suggest that children with FASD—even those on the mild end of the spectrum—show differences in their performance in the classroom when compared with peers. The results from this research validate the findings by several researchers (Carmichael Olson, Feldman, et al., 1998; Kodituwakku, 2007; Mattson & Riley, 2000; Thomas et al., 1998) indicating that the social/behavior problems associated with prenatal alcohol exposure do not appear to be solely the result of decreased cognitive functioning. This is the case because the children with FASD in the present research were matched with TD peers in their classrooms, and paired analysis revealed no significant differences between the groups with regard to IQ. Perhaps the children with FASD had other deficits that contributed to

their social communication problems tapped by the observational data. These deficits might have been in any number of areas, as discussed by Coggins and colleagues (2003) and Svensson (2006), such as deficiencies in language, attention, self-regulation, problem solving, and/or memory. We do know that for almost half the children with FASD in our sample, caregivers had noted some language and academic concerns. In a study by Greenbaum, Nulman, Rovet, and Koren (2002), 52 children who had been referred to a hospital-based outpatient program because of learning and behavior problems were split into two groups: 28 children with prenatal alcohol exposure (ARND group) and 24 children without prenatal alcohol exposure. Group comparisons revealed that the ARND group had lower scores on standardized measures of intelligence, language, and memory abilities than the nonalcohol group. Yet, the groups did not differ in the frequency of behavior or social problems as measured by The CBCL (Achenbach, 1991a). Greenbaum and colleagues' (2002) data suggest that children with ARND are likely to have neuropsychological deficits that characterize them but that social problems may not be significantly different from those of other children with learning and behavior problems. Our study isolated and documented the social differences between children with FASD and TD matched peers. Considering the findings of these two studies, perhaps the CNS involvement related to alcohol exposure can be manifested in a variety of ways, one of which is neuropsychological deficits with concomitant social problems. For children with language-learning problems or attention-deficit/hyperactivity disorder, studies suggest that their neurological impairments may contribute to problems in social interactions (Brinton & Fujiki, 1993; Bruce, Thernlund, & Nettelbladt, 2006; Fujiki, Brinton, Morgan, & Hart, 1999; Redmond & Rice, 1998). Children with FASD may share this characteristic. Clearly, future research is needed to address the underlying cause of social performance problems. Be that as it may, some children with FASD seem to stand out in regard to their interaction abilities with children, and this becomes an important aspect of their profile.

Clinical Implications

The data from this study provide a picture of performance of children with FASD as they interact with teachers and peers in the classroom. The data demonstrate the value of using a dimensional approach for documenting performance that might otherwise be challenging to depict. In turn, the results begin to explain why children with FASD—even those on the milder end of the continuum—are conspicuous to their teachers and why they may struggle in school. Direct observation served to enlighten the teacher report and, as such, contributed important information to the assessment process.

An important outcome of the observational methodology was recognizing the strengths as well as weaknesses of children with FASD as they interacted with others in the classroom. Prosocial/engaged behaviors were most common for children with known behavior problems. This directly speaks to the need for an ecobehavioral analysis of classroom performance for children with FASD—that is, determining those activities and factors that appear to facilitate prosocial/engaged performance. Such research would yield important information in regard to how teachers might engineer their classrooms to better support desired, on-task performance for children who face significant challenges in being successful. In regard to the children's off-task behaviors, such as irrelevant and passive/disengaged behaviors, investigating specific classroom factors that may influence performance would be a valuable exercise. As a component of intervention, classroom management, as suggested by Watson and Westby (2003), seems important. Without a doubt, the nature of the neuropsychological deficits that characterize children prenatally exposed to alcohol will create ongoing challenges to engagement in the classroom and deserve careful analysis.

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Children and Youth With Fetal Alcohol Spectrum Disorders: Summary of Intervention Recommendations After Clinical Diagnosis

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Abstract

Children with fetal alcohol spectrum disorders (FASDs) present with a wide range of developmental disabilities; however, clinical standards of care after a diagnosis are not well established. This retrospective review summarizes the types of intervention recommendations generated by an interdisciplinary FASD diagnostic team for 120 children ages 0.2 to 16.5 years receiving an FASD diagnosis at the University of Washington FAS Diagnostic & Prevention Network Clinic. Intervention recommendations documented in a FASD diagnostic summary report and submitted to each patient's medical record were subject to masked review and content analysis. Intervention recommendations were compared across 3 FASD diagnostic groups and selected demographic variables. The results show the type and frequency of services, supports, and resources recommended to a clinical sample of children with FASD.

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Prenatal alcohol exposure has a well-established and wide-ranging teratogenic impact on the central nervous system (CNS), with resultant impairments in learning, development, and adaptive function (Astley et al., 2009a; Riley & McGee, 2005). Fetal alcohol syndrome (FAS), a permanent birth defect characterized by a unique cluster of minor facial anomalies, CNS structural and/or functional abnormalities, and growth deficiency, is one of the more widely recognized outcomes of prenatal alcohol exposure. At 0.2 to 1.5 cases per 1,000 live births, FAS is the leading known preventable cause of developmental and intellectual disability (U.S. Centers for Disease Control and Prevention, 2006). However, FAS represents a relatively small proportion of children affected by prenatal alcohol exposure. The continuum of birth defects and developmental disabilities associated with alcohol exposure, currently referred to under the umbrella term of *fetal alcohol spectrum disorders* (*FASD*), may occur up to eight times as often as FAS among clinical populations of individuals with prenatal alcohol exposure (Astley, 2006). As such, FASD remains a significant public health concern that places substantial social and financial burdens on communities (Lupton, Burd, & Harwood, 2004).

A number of intervention guidelines and treatment strategies have been identified as useful for individuals with FASD and their families (Bertrand et al., 2004; Clarren, 2004; Kalberg & Buckley, 2007). Recently, several important evidence-based interventions also have emerged or are forthcoming (see Bertrand, 2009; Peadon, Rhys-Jones, Bower, & Elliott, 2009, for review). However, evidence-based standards of care for children and families following a diagnosis on the fetal alcohol spectrum remain limited (Olson, Jirikowic, Kartin, & Astley, 2007; Premji, Benzies, Serret, & Hayden, 2006). Moreover, caregivers continue to describe treatment barriers, unmet needs, and high levels of parenting stress (Olson, Oti, Gelo, & Beck 2009; D.M. Ryan, Bonnett, & Gass, 2006; S. Ryan & Ferguson, 2006). Difficulty qualifying for services, poorly coordinated services across systems and providers, gaps in the continuum of care, and a general paucity of specialized interventions for individuals affected by prenatal alcohol exposure are among the specific challenges reported.

Access to appropriate services and supports across all systems of care is a clearly stated need and a high priority among caregivers raising children with FASD and community professionals (Bertrand et al., 2004; Olson et al., 2009; D. M. Ryan et al., 2006; S. Ryan & Ferguson, 2006; Streissguth et al., 2004; Streissguth & O'Malley, 2000). Yet, the full scope of supports, services, and resources most needed by individuals who receive a diagnosis on the fetal alcohol spectrum have not been systematically described among large, clinically referred populations. As such, examining the type and frequency of clinical recommendations received by children and youths following a systematic diagnosis on the fetal alcohol spectrum is one means to better understand the unique needs of this population and to inform program development, research, and policy efforts.

The Washington state Fetal Alcohol Syndrome Diagnostic and Prevention Network (FAS DPN) was established in 1993. The network consists of four Washington-state, community-based clinics linked by the core research and training clinic at the University of Washington. The FAS DPN provides diagnostic evaluations using the FASD 4-Digit Diagnostic Code (Astley, 2004) administered by an interdisciplinary diagnostic team (Clarren, Olson, Clarren, & Astley, 2000). Currently, the FAS DPN clinical database contains more than 2,000 patient records with patient consent and institutional review board approval. With over 2,000 fields of information recorded per patient, the FAS DPN database is one of the largest and most comprehensive repositories of sociodemographic, cognitive–behavioral, and physical information for individuals of all ages and races–ethnicities with prenatal alcohol exposure, their families, and birth parents. Thus, it provides a rich source of information for a statewide clinical population of individuals systematically evaluated for FASDs.

An important component of the diagnostic process is to provide patients with a comprehensive set of intervention and/or follow-up recommendations specific to their needs. These recommendations are collectively generated by the interdisciplinary diagnostic team as part of the clinic visit after the FASD diagnostic evaluation. These recommendations include resources, referrals, and strategies that address presenting clinical concerns in areas such as health, behavior, social welfare, and education. Team members share these intervention recommendations with caregivers during a brief care conference and include the recommendations in the patient's FASD medical summary note that is submitted to the medical record.

A description of these recommendations, which have not been comprehensively analyzed to date, serves to provide insight into the types of interventions that may support the needs of children with FASDs and their caregivers at the time of diagnosis. The primary purposes of this study were to (a) describe the type and frequency of intervention recommendations provided to patients receiving a FASD diagnosis at a FASD diagnostic clinic and (b) determine if recommendations varied by FASD diagnostic groups and selected sociodemographic characteristics (e.g., age, gender, and caregiver status).

Method

Study Design

We completed a retrospective review of patient records from the University of Washington FAS DPN clinical database. The University of Washington Institutional Review Board approved the study.

Diagnostic Method

An interdisciplinary team (pediatrician, 2 psychologists, occupational therapist, speech–language pathologist, family advocate, and social worker) used the FASD 4-Digit Diagnostic Code to derive the FASD diagnoses (Astley, 2004; Astley & Clarren, 2000). Table 1 outlines key phases of the diagnostic process and primary sources of clinical data used to derive the diagnoses (Clarren et al., 2000). Although the FAS DPN database is a clinic-referred sample, the only requirement for obtaining a diagnostic evaluation is confirmed prenatal alcohol exposure of any quantity, frequency, or duration.

The FASD 4-Digit Diagnostic Code is an objective, case-defined diagnostic system. The four digits of the code reflect the magnitude of expression of the four key diagnostic features of FASD in the following order: (a) growth deficiency, (b) FAS facial features, (c) CNS structural–functional abnormality, and (d) prenatal alcohol exposure. The magnitude of expression of each feature is ranked independently on a 4-point Likert scale, with 1 reflecting complete absence of the FAS feature and 4 reflecting a strong "classic"

Table 1. Overview of FAS DPN Diagnostic Process and Sources of Clinical Data

Phase	Description
Phase 1	*Clinical intake:* Caregivers complete a comprehensive "New Patient Information Form" prior to the clinic visit to report current concerns and developmental, social and alcohol exposure history. Past medical, educational, psychological, social, and legal records are also obtained.
	Record review: Psychologist reviews all available medical, developmental, and educational records and presents a case summary to the FASD diagnostic team on the day of the diagnostic evaluation.
Phase 2	*Psychometric screening/evaluation*: Diagnostic team members (occupational therapist, psychologist, speech–language pathologist) screen/assess the patient's current neurobehavioral performance (e.g., language and communication, executive function, cognition, sensory–motor skills).
	Physical examination: Physician examines diagnostic parameters of growth and facial dysmorphology (and general health).
	Caregiver(s) interview: Pediatrician and psychologist conduct a 2-hr caregiver interview to query about past and present child behavior, developmental concerns, and the child's current level of function.
Phase 3	*Diagnosis and intervention recommendations*: Diagnostic team reviews and synthesizes data, derives the 4-Digit Code, and generates intervention recommendations.
	Diagnostic summary: Diagnostic team shares the diagnosis and intervention recommendations with caregiver(s) in a brief case conference.
	Diagnostic summary report: Diagnosis, assessment results, and intervention recommendations are integrated into a comprehensive 6–8-page diagnostic summary report and submitted to the patient's medical record.

Note. FAS DPN = Washington state Fetal Alcohol Syndrome Diagnostic and Prevention Network; FASD = fetal alcohol spectrum disorders.

presence of the FAS feature. There are 256 possible 4-Digit Diagnostic Codes, ranging from 1111 to 4444. Each 4-Digit Diagnostic Code falls into 1 of 22 (labeled A–V) unique clinical diagnostic categories. Seven (A–C; E–H) of the 22 diagnostic categories fall broadly under the designation of FASD (A. FAS–alcohol exposed; B. FAS–alcohol exposure unknown; C. partial FAS–alcohol exposed; E and F. static encephalopathy–alcohol exposed; G and H. neurobehavioral disorder–alcohol-exposed). See Astley (2004) for a full description of the 4-Digit Diagnostic Code and diagnostic categories.

Study Population

We applied the following inclusion criteria to the FAS DPN clinical database to establish the study sample: (a) chronological ages, birth through 18.9 years; (b) received a FASD diagnostic evaluation at the core University of Washington FAS DPN clinic between January 2001 and June 2007; (c) received a 4-Digit Diagnostic classification of FAS with confirmed or unknown alcohol exposure, partial FAS–alcohol exposed (pFAS), static encephalopathy–alcohol exposed (SE/AE), or neurobehavioral disorder–alcohol exposed (ND/AE); and (d) signed a consent to allow the use of their clinical data for research purposes. We used records from the core University of Washington FAS DPN clinic because they represented a patient group with clinical recommendations that were procedurally consistent and fully documented in the patients' diagnostic summary reports. Records from 2001 to 2007 contained the most current intervention needs and service availability. Initially, we considered adult patient records for the study but ultimately excluded them because of the relatively small proportion of patients older than 18 years of age seen in the diagnostic clinic.

One hundred ninety patient records met eligibility criteria. From these records, we established three study groups based on 4-Digit Code

diagnostic outcomes. Children in Group 1 had FAS or partial FAS (FAS/pFAS): significant cognitive–behavioral dysfunction with the FAS facial phenotype (n = 40). Children in Group 2 had static encephalopathy, alcohol exposed (SE/AE): significant cognitive–behavioral dysfunction broadly comparable with Group 1 but no FAS facial phenotype (n = 65). Children in Group 3 had neurobehavioral disorder, alcohol exposed (ND/AE): mild to moderate cognitive–behavioral dysfunction and no FAS facial phenotype (n = 85). Previous research has confirmed these three diagnostic subgroups are clinically distinct and span the full continuum of FASD (Astley et al., 2009a).

To balance age, gender, and race–ethnicity across the three FASD study groups, we started with the smallest of the three study groups (FAS/pFAS; n = 40) and selected an equal number of records (40 per group) from the eligible SE/AE and ND/AE groups by pair matching on age (within 6 months), gender, and race–ethnicity to each case in the FAS/pFAS group. If multiple records met matching criteria we randomly selected a single record.

Content Analysis

For each patient record reviewed, we examined only the portion of the FASD diagnostic summary report containing the clinical intervention recommendations. We used masked review and content analysis to develop a standard coding scheme for categorizing recommendations (Waltz, Strickland, & Lenz, 2005). The first two authors (T. J. and J. G.), both FASD diagnostic team members for over 13 years, developed the first draft of the coding scheme by reviewing 20 randomly selected, eligible patient recommendation reports (not included in the final study sample). Three additional diagnostic team members from different professional disciplines (e.g., psychology, social work) provided expert review of the clinical relevance, clarity, and completeness of the coding scheme. The first two authors (T. J. and J. G.) revised the coding scheme and assessed interrater reliability on 20 additional eligible patient records (not included in the final sample). After the coding scheme was finalized, the first author (T. J.) used it to code all 120 patient recommendation records (masked to their diagnostic outcome) in the study. Table 2 illustrates the coding scheme with category and subcategory definitions and examples of coded text from the diagnostic summary reports.

Data Analysis

The primary focus of the analysis was to determine if intervention recommendations differed significantly among FASD diagnostic groups, caregiver status, and across age groups. Descriptive statistics (Ms, *SD*s, and proportions) were used to summarize sociodemographic and cognitive variables, and intervention recommendation categories across study groups. Analyses of variance (ANOVAs) and chi-square tests were used to compare means and proportions, respectively, among the study groups. Significance levels were set at a conventional two-tailed alpha (α = .05). Analyses were exploratory, with no adjustment for multiple comparisons, thus p values should be interpreted accordingly.

Results

Sociodemographic Characteristics

The mean age of the total sample was 6.5 years (*SD* = 4.1), with a range of 0.2 to 16.5 years; 53% were male and 60% were Caucasian. Sociodemographic characteristics of this sample were comparable with the entire statewide sample of FAS DPN patients (N = 1,235) less than 19 years of age seen since 1993 with similar FASD diagnostic classifications (M age = 8.0 years, *SD* = 4.1; 59% male; 49% Caucasian). Sociodemographic and clinical characteristics of the study sample by FASD diagnostic group are presented in Table 3.

At least 56% of children in the sample had confirmed exposure to high levels of alcohol (i.e., 4-Digit Code, Alcohol Scale Rank 4, indicating an exposure pattern consistent with the medical literature placing the fetus at high risk. The remaining 44% of the sample had confirmed exposure, but the actual levels of exposure were low to moderate or unknown (i.e., 4-Digit Code, Alcohol Scale Rank 3; Astley, 2004). Other reported prenatal risk factors included in utero exposure to illicit drugs (70%) and/or tobacco (71%). Eighty-five (71%) children also experienced notable postnatal risk factors. For example, among these 81 children, 55% experienced physical abuse and 31% had been in one or more out-of-home placements. Approximately 30% of the sample had a reported diagnosis of attention deficit disorder with or without hyperactivity. In general, these other risk factors were distributed comparably across the three diagnostic study groups, with one

Table 2. Coding Scheme and Sample Recommendations From Diagnostic Summary Report

Recommendation category and definition	Subcategories	Sample content from diagnostic summary report
1. *Accommodations:* Specific adaptation or modification to environment/routine to be implemented in home, school, or other setting.	1. Behavior/emotional regulation (e.g., supports for group participation, enhancing environmental structure) 2. Communication (e.g., visual schedules, cues for social interaction) 3. Executive function, organization, memory (e.g., memory aids, checklists) 4. Sensory–motor (e.g., headphones, reducing sensory input, keyboarding) 5. Team communication (e.g., communication between home, school, and other providers)	Code: 1.1 "Based on observations made in clinic today, this team recommends the use of visual strategies and supports to help James maintain attention and manage his behavior."
2. *Anticipatory guidance/prevention*: Prevention oriented recommendations based on developmental risk factors for future problems.	1. Substance abuse prevention 2. Learning problems/behavior risks (awareness of potential for school/learning difficulties and/or mental health problems) 3. Reproductive health (e.g., pregnancy and STD prevention)	Code: 2.1 "James is at high risk for substance abuse later in life, developmentally appropriate substance abuse education that occurs early and often is critical for future prevention.
3. *Community-based:* Leisure or recreation recommendations for specific, community-based activities/programs that are prosocial, recreational, extracurricular in nature and include appropriate developmental and social supports.	1. Prosocial extracurricular/play activities (e.g., Boys and Girls Club; community social skills groups) 2. Physical/movement (e.g., noncompetitive sports; therapeutic horseback riding; Special Olympics) 3. Special interest groups (e.g., focused leisure, religious, or cultural activities) 4. Adult mentor (e.g., Big Brother/Big Sister)	Code: 3.2 "Structured physical activity, such as swimming lessons and/or gymnastics is recommended to help develop balance and gross motor skills."
4. *Education/assessment:* Referral, advocacy, or support for a specific educational program or service, psychoeducational assessment, or specific skill area that requires educational monitoring.	1. Referral/support for educational service (e.g., special education, life skills training, birth to 3 year program) 2. Monitor a specific area of performance (e.g., fine motor, language) 3. Psychoeducational–neuropsychological assessment to determine special education eligibility, re-examine individual education plan or advocate for continued eligibility	Code: 4.1 "Sarah's level of adaptive functioning remains quite low. Continued attention to adaptive living skills is strongly recommended. We strongly recommend that Sarah's special education services remain intact as she moves into middle school as we anticipate that this transition will require increased support."

Table 2. Continued

Recommendation category and definition	Subcategories	Sample content from diagnostic summary report
5. *Family support–resources:* Referral/ recommendations for educational materials (e.g., books, Web sites) community support groups, advocacy training, or caregiver education or support.	1. Books, Web-based resources (e.g., attachment, sleep, FASD) 2. Personal/peer support (e.g., National Organization or Fetal Alcohol Syndrome [NOFAS], grandparent support group) 3. Advocacy/education (e.g., parent advocacy group, parent education, community training) 4. Respite/self-care for caregiver	Code 5.2 and 5.4 "We recommend continued personal, professional and peer support for parents through organizations such as NOFAS Washington for advocacy and training. We strongly encourage parents to pursue avenues for self-care, including respite care to help them continue parenting as effectively as possible."
6. *Medical:* Recommendation/referral to medical specialist or current provider for evaluation or follow-up care regarding a specific medical problem or issue.	1. Psychiatric services and/or medication management/consultation 2. ADHD evaluation 3. Sleep evaluation 4. Vision/hearing evaluation 5. Growth 6. Neurological evaluation/consultation 7. Genetic work up or consultation	Code 6.3 "Consultation with a sleep specialist with an overnight sleep study may reveal primary sleep issues impacting late bedtimes, nap refusal and sleep behaviors. Code 6.5 A thorough nutritional assessment to assess failure to thrive is recommended."
7. *Mental health:* Support/referral for mental health services to address individual and/or family needs around behavior, development, or mental health problem.	1. Behavioral consultation or specialist (e.g., behavior management, home-based intervention services) 2. Individual counseling 3. Family counseling 4. Case management	Code 7.3 "Beth and her family may benefit from counseling. They have done a wonderful job with this complex child but may need support for her behavioral and cognitive issues as she goes through adolescence."
8. *Developmental therapy:* Referral/recommendation for occupational therapy, physical therapy, speech–language therapy, or specific therapeutic program.	1. Referral/recommendation for occupational, physical, or speech language therapy evaluation or treatment 2. Referral to a therapeutic social skills group	Code 8.1 "Language assessment indicates difficulties with unstructured communication, increasing risk for future academic and social problems. An evaluation by an SLP can help determine if reading and writing difficulties have a basis in language impairment."

Table 2. Continued

Recommendation category and definition	Subcategories	Sample content from diagnostic summary report
9. *Safety* Recommendations/resources to address home, school, or community safety concerns.	1. Personal ID/safety (e.g., ID bracelet, wallet card 2. Environmental modification/supervision (e.g., alarms, line-of-sight supervision)	Codes 9.2 and 9.1 "Because of personal safety issues we recommend that Mary should be in line of sight supervision at all times, in all settings and we recommend that she wear an ID bracelet."
10. *Social service/child welfare:* Resources/support for children in out of home placements, including caregiver support and funding resources.	1. Placement advocacy (e.g., stable, safe, structured, supportive home environment; movement towards long-term permanency) 2. Caregiver resources to support appropriate placements and long-term needs (e.g., adoption support, supplemental security income eligibility, family support program)	Code 10.1 "Chris would benefit from a stable home environment with structured daily activities. The new foster, and prospective adoptive parents, will need support and education for complex health and behavioral needs.
11. *Other*	1. Substance abuse recommendations supporting treatment or recovery (caregiver or patient). 2. FASD re-evaluation 3. Other	Code 11.1 "The team highly recommends that Eric's mother continue to access her social and sobriety supports."

Note. FASD = fetal alcohol spectrum disorders; ADHD = attention deficit hyperactivity disorder.

Table 3 Sociodemographic and Cognitive Profiles by Diagnostic Group

Variable	FAS/pFAS (n = 40)	SE/AE (n = 40)	ND/AE (n =40)	Test statistic
Sex: *n* (%)				
Male	20 (50)	23 (58)	21 (53)	$\chi^2 = 0.47$
Female	20 (50)	17 (42)	19 (47)	
Age (years)				
M (*SD*)	6.3 (4.2)	6.8 (4.1)	6.4 (4.1)	$F = 1.70$
Range	0.4–16.5	0.2–15.4	0.4–15.8	
Age (group): *n* (%)				
0–2 years	8 (20)	9 (23)	8 (20)	$\chi^2 = 5.90$
3–5 years	16 (40)	7 (18)	14 (35)	
6–11 years	11 (28)	18 (45)	13 (33)	
12–17 years	5 (13)	5 (13)	5 (13)	
Race/ethnicity: *n* (%)				
Caucasian	24 (60)	24 (60)	24 (60)	$\chi^2 = 0.03$[a]
African American	7 (18)	5 (13)	6 (15)	
Native American	4 (10)	6 (15)	7 (18)	
Other	5 (13)	5 (13)	3 (8)	
Primary Caregiver: *n* (%)				
Biological mother	3 (8)	5 (13)	6 (15)	$\chi^2 = 2.97$
Foster	18 (45)	11 (28)	14 (35)	
Adoptive	9 (23)	13 (33)	9 (23)	
Other relative	10 (25)	11 (28)	11 (28)	
Highest maternal education (reported): *n* (valid %)	(n = 26)	(n = 28)	(n = 25)	
Some HS	15 (58)	16 (57)	15 (60)	$\chi^2 = 0.002$[b]
HS graduate	8 (31)	9 (32)	8 (32)	
Some college	2 (8)	3 (11)	2 (8)	
College degree	1 (4)	0 (0)	1 (4)	
IQ	(n = 20)	(n = 24)	(n = 21)	
M (*SD*)	81.0 (16.1)	83.8 (13.1)	96.8 (15.4)	$F = 6.64$**
Range	60–120	60–103	66–135	

Note. FAS/pFAS = fetal alcohol syndrome/partial fetal alcohol syndrome; SE/AE = static encephalopathy, alcohol-exposed; ND/AE = neurobehavioral disorder, alcohol-exposed; HS = high school.
[a]The groups were collapsed into Caucasian/non-Caucasian to adjust for small samples in some cells. [b]The groups were collapsed into high school graduate or not high school graduate to adjust for small samples in some cells.
*$p < .05$. **$p < .01$.

exception. Children with SE/AE (42%) and ND/AE (36%) were significantly more likely to present with other psychiatric diagnosis (e.g., oppositional defiant disorder, reactive attachment disorder) compared with those with FAS/pFAS (13%), $\chi^2(2, N = 114) = 8.49$, $p = .01$. The high prevalence of other prenatal and postnatal adverse exposures and events observed in this study sample were comparable with the prevalence observed in the entire FAS DPN clinical sample.

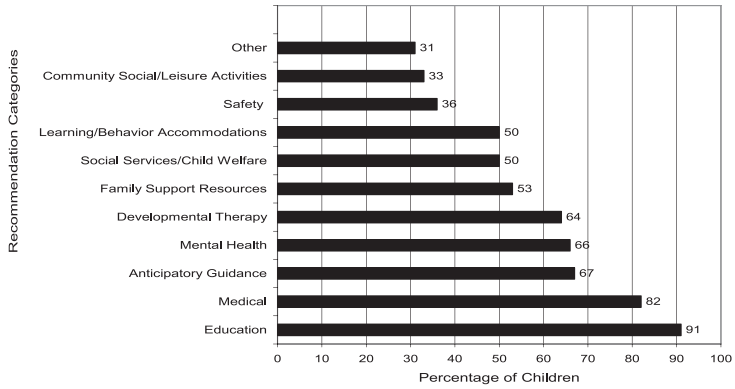

Figure 1 Percentages of children and youths with fetal alcohol spectrum disorders (FASD; $n = 120$) receiving one or more recommendations by category.

Coding Scheme and Interrater Agreement

The final coding scheme (see Table 2) consisted of 11 primary intervention categories each with respective subcategories. Interrater agreement between the first two authors (T. J. and J. G.) on the 11 primary categories exceeded 90%. Intrarater agreement on 11 (10%) records from the final sample was 94%; interrater agreement compared with a masters-level clinical trainee (who was not a diagnostic team member) was 90%.

Primary Intervention Recommendations

The proportion of children with FASD from the entire sample receiving one or more recommendations across each of the 11 primary intervention categories is profiled in Figure 1. The majority of children in this sample received one or more recommendations targeting educational needs. Comprehensive psychoeducational or neuropsychological assessments (50%); special education programs, services, or eligibility (40%); or advocacy to enhance or modify existing educational programs or services (28%) were the most frequent recommendations in the education category. The medical needs of children with FASD in this sample were also high. Medical referrals and recommendations reflected needs for psychiatric care and/or medication management (35%); vision and/or hearing screening (30%); neurological consultation or treatment (22%); attention deficit disorder/attention deficit hyperactivity disorder evaluation or treatment (20%); and growth–small stature (17%), sleep medicine (14%), or genetic (13%) evaluation or consultation.

Approximately two thirds of children and youth in this sample received mental health, developmental therapy, and/or anticipatory guidance recommendations. Individual counseling (33%), family counseling (20%), or specialized behavior management support (18%) constituted the majority of mental health recommendations. Speech–language assessment or intervention (50%), occupational therapy or physical therapy assessment or intervention (50%), or therapeutic social skills groups (12%) were the most frequent types of developmental therapy services recommended. Substance abuse prevention (51%), prospectively monitoring risks for learning and/or behavioral problems (32%), and attention to reproductive health and safety (e.g., pregnancy prevention; 13%) were the anticipatory guidance recommendations provided most often.

About half of the children and youths received one or more recommendations for family support resources, social service–child welfare support, or learning or behavior accommodations. Caregiver support groups (36%), printed or electronic resources (20%), advocacy training and education (16%), and respite or "self-care" (10%) were the most frequent family resource recommendations. Supportive fiscal resources for caregivers (30%) and advocacy for stable, timely, and appropriate home placements (26%) composed most of the social service or child welfare recommendations. Instructional or behavioral accommodations included

Table 4 Percentages of Children and Youths Receiving One or More Intervention Recommendations by Category Across Diagnostic Groups

Recommendation category	FAS/pFAS (n = 40): n (%)	SE/AE (n = 40): n (%)	ND/AE (n = 40): n (%)
Accommodations[a]	26 (65)	21 (53)	13 (33)
Anticipatory guidance	25 (63)	24 (60)	31 (78)
Community-based program	17 (43)	10 (25)	13 (33)
Education[b, c]	40 (100)	36 (90)	33 (83)
Family support resources	23 (56)	22 (55)	18 (45)
Medical	33 (83)	32 (80)	33 (83)
Mental health	28 (70)	24 (60)	27 (68)
Developmental therapy	26 (60)	25 (63)	26 (65)
Safety	14 (35)	15 (38)	14 (35)
Social services/child welfare	22 (55)	19 (48)	19 (48)
Other[d]	18 (45)	8 (20)	12 (30)

Note: FAS/pFAS = fetal alcohol syndrome/partial fetal alcohol syndrome; SE/AE = static encephalopathy, alcohol-exposed; ND/AE = neurobehavioral disorder, alcohol-exposed
[a]Significant contrast, FAS/pFAS vs. ND/AE: $\chi^2(1, N = 80) = 8.45$ $p = .004$. [b]Significant contrast, FAS/pFAS vs. ND/AE: $\chi^2(1, N = 80) = 7.67$ $p = .006$. [c]Significant contrast, FAS/pFAS vs. SE/AE: $\chi^2(1, N = 80) = 4.21$ $p = .04$. [d]Significant contrast, FAS/pFAS vs. SE/AE: $\chi^2(1, N = 80) = 5.70$ $p = .02$.

recommendations for team communication among caregivers and providers (25%) and specific strategies to support learning or behavior in response to executive function (17%), behavior regulation (16%), sensory–motor (14%), or communication (7%) challenges or impairments.

Strategies to enhance personal safety or participate in community-based recreation or leisure activities were important but less frequent recommendations. Procuring personal identification (e.g., ID bracelet; 21%) or enhancing features of the physical (e.g., alarms) or social environment (e.g., line-of-sight supervision; 20%) were among the primary safety interventions made by this team. Referrals to local youth groups, clubs, or programs to facilitate prosocial and/or leisure skill development (23%), physical development (e.g., Special Olympics) (18%), or provide opportunities for adult mentorship (6%) constituted community-based leisure or recreation recommendations.

Primary Intervention Recommendations: Group Contrasts

Table 4 presents the percentages of children receiving one or more primary intervention recommendations by FASD diagnostic group. Intervention recommendations were relatively comparable across the three diagnostic groups, with three exceptions. Children with FAS/pFAS or SE/AE were significantly more likely than children with ND/AE to receive specific instructional or behavioral accommodations. Significantly more children with FAS/pFAS than children with ND/AE received education recommendations. Last, significantly more children with FAS/pFAS than SE/AE received recommendations categorized as *other* ($p <$ .05). Recommendations coded as *other* included substance abuse treatment or recovery support for the patient or caregiver, referrals for research studies, or consultation with a diagnostic team member.

Important developmental trends emerged when recommendations were analyzed across four age categories. Figure 2 illustrates recommendations that were significantly different across age groups. A higher proportion of children in the youngest age group (birth–2 years) received recommendations for family support resources, $\chi^2(3, N = 120) = 11.37$, $p = .010$, and social service–child welfare interventions, $\chi^2(1, N = 120) = 20.79$, $p = .000$, compared with children in older age groups. Mental health recommendations and referrals to community-based programs for prosocial recreation or leisure activities, $\chi^2(3, N = 120) = 16.27$, $p =$

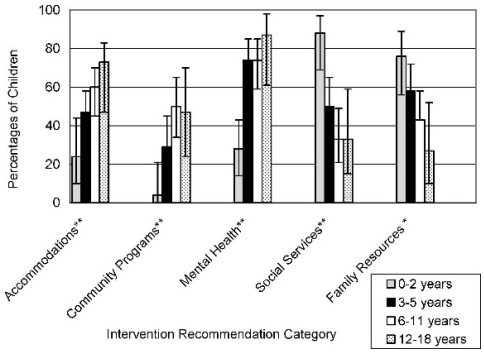

Figure 2 Percentages of children and youth receiving one or more intervention recommendations: significant trends by age group. Error bars indicate 95% confidence interval. *$p \leq .01$. **$p \leq .001$.

.001, were notably higher among children 3 years and older than infants and toddlers (birth–2 years), $\chi^2(3, N = 120) = 11.57$, $p = .009$. Specific behavioral or instructional accommodations also increased with age, with the highest proportion seen among children in the oldest age group (12–18 years), $\chi^2(3, N = 120) = 11.57$, $p = .009$. Figure 3 illustrates recommendations that were comparable across age groups.

Overall, intervention recommendations were relatively consistent across caregiver status (i.e., biological mother, foster parent, adoptive parent, or other) with two exceptions. Children with a foster caregiver were significantly more likely to receive social service–child welfare recommendations than children with adoptive parents, $\chi^2(1, N = 74) = 15.48$, $p = .001$; birth parents, $\chi^2(1, N = 57) = 6.00$, $p = .014$; or other caregivers, $\chi^2(1, N = 75) = 3.83$, $p = .05$. In addition, children in the care of an adoptive parent were significantly more likely to receive recommendations for community-based leisure or prosocial recreational activities than foster caregivers, $\chi^2(1, N = 74) = 4.94$, $p = .03$, although more than half of children living with their birth mothers also received recommendations in this category. The type and frequency of recommendations were generally consistent across gender for the entire sample. One exception was that females were significantly more likely (82%) to receive one or more recommendations categorized as anticipatory guidance than males (53%), $\chi^2(1, N = 120) = 11.32$, $p = .001$.

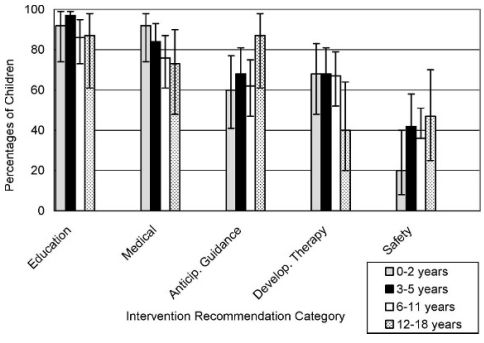

Figure 3 Percentages of children and youth receiving one or more intervention recommendations: nonsignificant trends by age group. Error bars indicate 95% confidence interval.

Discussion

This retrospective analysis sheds light on the type and frequency of supports, services, and referrals recommended by an interdisciplinary diagnostic team for children and youths who received a FASD diagnosis. Findings indicate that children with FASD, like children with other neurodevelopmental disabilities, have a wide range of complex and specialized needs that span across systems of care. Although FAS has historically been considered among the most severe outcomes of prenatal alcohol exposure, these data show that similar intervention recommendations and needs were seen for children across the fetal alcohol spectrum, regardless of diagnosis.

Several important developmental trends also emerged. Though not surprising, this is notable because children with FASD are often diagnosed at different ages, and some disabilities associated with prenatal alcohol exposure may not be evident until school age. Furthermore, a large proportion of children in this sample experienced other prenatal (e.g., exposure to tobacco or illicit drugs) and postnatal (e.g., multiple home placements, abuse, neglect) risks. Although these children received a diagnosis under the umbrella of FASD, prenatal alcohol exposure was clearly not the only risk factor that may have impacted their development and needs at the time of diagnosis. Detailed neuropsychological, behavioral, and mental health profiles

of children from the same clinical population with the same FASD diagnostic classifications (FAS/pFAS, SE/AE, and ND/AE) have been described by Astley et al. (2009b) and provide more perspective on the needs and developmental challenges underlying these clinical recommendations.

The large percentage of children receiving educational recommendations reflects the well-substantiated and elevated risks associated with prenatal alcohol exposure and learning and academic achievement for individuals across the fetal alcohol spectrum (Riley & McGee, 2005; S. Ryan & Ferguson, 2006). Comprehensive developmental or educational assessments were frequently recommended as a means to more thoroughly evaluate neurobehavioral or neurocognitive concerns impacting school performance. Although the amount of neuropsychological and behavioral assessment data available at the time of the diagnostic evaluation is sufficient to render an accurate diagnosis, a child will often benefit from additional neuropsychological–behavioral assessments to guide individualized intervention efforts. Special education programs and services were also noticeably perceived as necessary sources of academic support for many children with FASD, but the need to consider alternative instructional approaches, monitor academic risks, or advocate for specific interventions (e.g., transition support, functional behavior analysis) was evident.

The learning and behavior accommodations we provided these children give additional insight into the neurobehavioral challenges experienced by children with FASD. The types of accommodation strategies recommended were congruent with domains (e.g., communication, executive function, sensory–motor, and behavior regulation) commonly associated with the adverse effects of prenatal alcohol exposure (Astley et al., 2009b, Church & Kaltenbach, 1997; Coggins, Olswang, Olson, & Timler, 2003; Jirikowic, Olson, & Kartin, 2008; Rasmussen, 2005; Riley & McGee, 2005). The scope and variability of the accommodation strategies identified within each neurobehavioral domain also underscore the need for interdisciplinary approaches to diagnosis, assessment, and intervention.

Service providers should be aware of and prepared to consider an array of educational resources, supports, and services for children with FASD. Emerging evidence supports the use of targeted instructional strategies for children with FASD (e.g., for mathematics, safety, and social skills; Kable, Coles, & Taddeo, 2007; O'Connor et al., 2006) as well as behavioral interventions that provide caregiver education, behavioral reframing, and environmental accommodations (Olson et al., 2005). Differentiated instruction, accommodations that enhance external structure and environments (e.g., visual supports), and learning and functional expectations congruent with neurobehavioral abilities appear to be meaningful and important treatment considerations for children with FASD (Clarren, 2004; Kalberg & Buckley, 2007).

Referrals for primary and specialized medical care also constituted a large proportion of the intervention recommendations we made. Several concomitant health, developmental, and psychopathological concerns among this group of children with FASD were revealed. The types of referrals and services that were often advised reflect body structures and functions reported as more vulnerable to the teratogenic impact of prenatal alcohol exposure (e.g., vision, hearing, CNS) as well as the adverse and cumulative impact of other prenatal and postnatal risk factors (Stratton, Howe, & Battaglia, 1996). As such, these findings alert providers to areas of health and development that may benefit from screening, as well as referrals to, and/or treatment by appropriate medical specialists.

A clear need for mental health services, particularly for children older than 3 years of age with an upward trend through adolescence, also emerged. As in other studies of individuals with FASD, mental health or psychiatric conditions were reported across the full range of diagnosis in this sample (Astley et al., 2009b; Streissguth & O'Malley, 2000; Streissguth et al., 2004). Prenatal alcohol exposure has also been considered a risk factor for attachment problems and later psychopathology (O'Connor et al., 2002; O'Connor & Paley, 2006). As such, infant mental health interventions, which have been found useful among other biologically and ecologically vulnerable children (Fisher, Gunnar, Dozier, Bruce, & Pears, 2006) warrant more attention and research among young children with prenatal alcohol exposure and FASD.

Despite a lack of formal infant mental health services, advocacy for important protective factors early in life (Streissguth et al., 2004) were among the social service– or child welfare–related recommendations received by many of the youngest children. As expected, a higher proportion of these

recommendations were received by children in foster care at the time of the diagnostic evaluation, presumably to optimize responsive and stable caregiving environments.

Although parent education and family support resources were a clear priority for caregivers of young children, the frequency of these recommendations did not occur uniformly across older age groups in this sample. This is surprising because education and resources to support and empower caregivers and families are important considerations for parents of children with disabilities across all ages and through different stages of development (Douma, Dekker, & Koot, 2006). One possible explanation is that caregiver education and support are inherent throughout the diagnostic process of this clinic; therefore, the breadth of caregiver support provided was not formally documented for all patients.

Last, diagnosis also serves as an important point of intervention for anticipatory guidance and primary prevention. Although most children and caregivers received some type of anticipatory guidance during their clinic visit, only about half of the children and youth across the entire sample received specific recommendations for substance abuse prevention. As a recognized and critical need with this population, developmentally appropriate substance abuse education that occurs early and often in life has since become a standard recommendation for all patients in this diagnostic clinic.

Findings need to be considered within the context of several study limitations. The recommendations were generated by a diagnostic team within the context of a tertiary care setting. Recommendations were made in the geographic context of a large metropolitan area; therefore, they reflect, in part, the availability of local programs, services, and resources at the time of diagnosis. These factors may limit generalizability of findings. However, this study is the first to describe clinically derived intervention recommendations using a large, representative, clinical sample of children from a Washington-state FASD diagnostic specialty clinic. As such, these results profile and benchmark child and family needs and priorities identified during a FASD diagnostic assessment, a critical point in the continuum of care for individuals affected by prenatal alcohol exposure.

Results from this descriptive study raise several questions regarding the outcomes of these intervention recommendations. Future research should investigate the success with which families access and implement the recommended services, resources, and supports after receiving an alcohol-related evaluation and diagnosis. The perceived short- and long-term value of the intervention recommendations should also be investigated, as developmental needs often change over time. Furthermore, the supports and services needed by adults with FASD remain important to examine, given the lifelong disabilities associated with FASD.

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ENCYCLOPEDIA on Early Childhood Development

FETAL ALCOHOL SPECTRUM DISORDERS (FASD)

Clinical Assessment of Individuals with Fetal Alcohol Spectrum Disorders (FASD)

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Introduction

Fetal Alcohol Syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. The condition is characterized by growth deficiency, a unique cluster of minor facial anomalies and central nervous system (CNS) abnormalities.[1] The prevalence of FAS is estimated to be 1-3/1,000 live-births[1] in the general population, and as high as 10-15/1,000 in high-risk populations like foster care.[2] Not all individuals exposed and damaged by alcohol have FAS. Most present neuropsychological impairments without the physical findings. The condition is now recognized as a spectrum of disorders, FASD. Diagnoses like FAS, Partial FAS (PFAS), Alcohol-Related Neurodevelopmental Disorder (ARND), Static Encephalopathy/Alcohol - Exposed (SE/AE) and Neurobehavioural Disorder/Alcohol-Exposed (ND/AE) fall under the umbrella of FASD.[1,3]

Subject

Although reference to the harmful effects of maternal drinking on infant outcome date back to biblical times,[4,5,6] the term FAS was not coined until 1973.[7-9,10,11] Diagnostic guidelines were developed and refined through the 70s and 80s,[7,12,13,14] culminating in 1996 with the publication of the Institute of Medicine (IOM) guidelines.[1] While the IOM guidelines reflected an important advancement, the IOM committee continued to feel: 1) "a medical diagnosis of FAS remained the purview of dysmorphologists and clinical geneticists," and 2) the guidelines remained intentionally broad and conceptual (gestalt) rather than specific and operational (case-defined).[15,16] For example, the guidelines for CNS dysfunction did not address how many areas of deficit must be present or how severe the deficits must be. The guidelines for the facial phenotype did not address how many features must be present, how severe each feature must be, or what measurement scales should be used to judge their severity. And introduction of the term ARND ran counter to the retraction of the term Fetal Alcohol Effects (FAE) the year prior.[17] Overall, guidelines through 1996 were not sufficiently specific to ensure diagnostic accuracy (the ability to derive the correct diagnosis) or diagnostic reproducibility (the ability for two different clinicians to derive the same diagnosis in a given patient).[18]

Problems

In the absence of an accurate/reproducible method of diagnosis, diagnoses continued to vary widely between clinics.[1,18,19] From a clinical perspective, diagnostic misclassification leads to inappropriate patient care, increased risk for secondary disabilities[20] and missed opportunities for prevention.[15,21,22] From a public health perspective, diagnostic misclassification leads to inaccurate prevalence estimates.[15] Inaccurate estimates thwart efforts to allocate sufficient social/educational/medical services to this high-risk population and preclude the accurate assessment of prevention efforts. From a research perspective, diagnostic misclassification prevents detection of clinically-meaningful contrasts between groups and valid comparisons of outcomes between studies.[23]

Research Context

To overcome the limitations of the physician-focused gestalt approach to FASD diagnosis, the FASDPN introduced an interdisciplinary team approach in 1993 (medical doctor, psychologist, speech-language pathologist and occupational therapist)[24,25] guided by a rigorous, case-defined set of guidelines (FASD 4-Digit Diagnostic Code) in 1997.[15,16] Briefly, the 4 digits of the 4-Digit Code reflect the magnitude of expression of the 4 key diagnostic features of FASD in the following

order: 1) growth deficiency, 2) FAS facial phenotype, 3) CNS structural/functional abnormalities, and 4) prenatal alcohol exposure (Fig. 1).[15] The magnitude of expression of each feature is ranked on a 4-point scale, with 1 reflecting complete absence of the feature and 4 reflecting severe presence of the feature. Each rank is specifically case-defined. The 4-Digit codes range from 1111 to 4444. To date, every combination of Code has been observed in the FASDPN clinics, reflecting the true diversity of outcome associated with prenatal alcohol exposure. The subset of 4-Digit Codes that fall under the umbrella of FASD can be grouped into three clinically meaningful and distinct diagnostic subgroups:

1. FAS/PFAS (severe neuropsychological impairment with the FAS facial phenotype);
2. SE/AE (severe neuropsychological impairment without the facial phenotype); and
3. ND/AE (moderate neuropsychological impairment without the facial phenotype).[23,26,27]

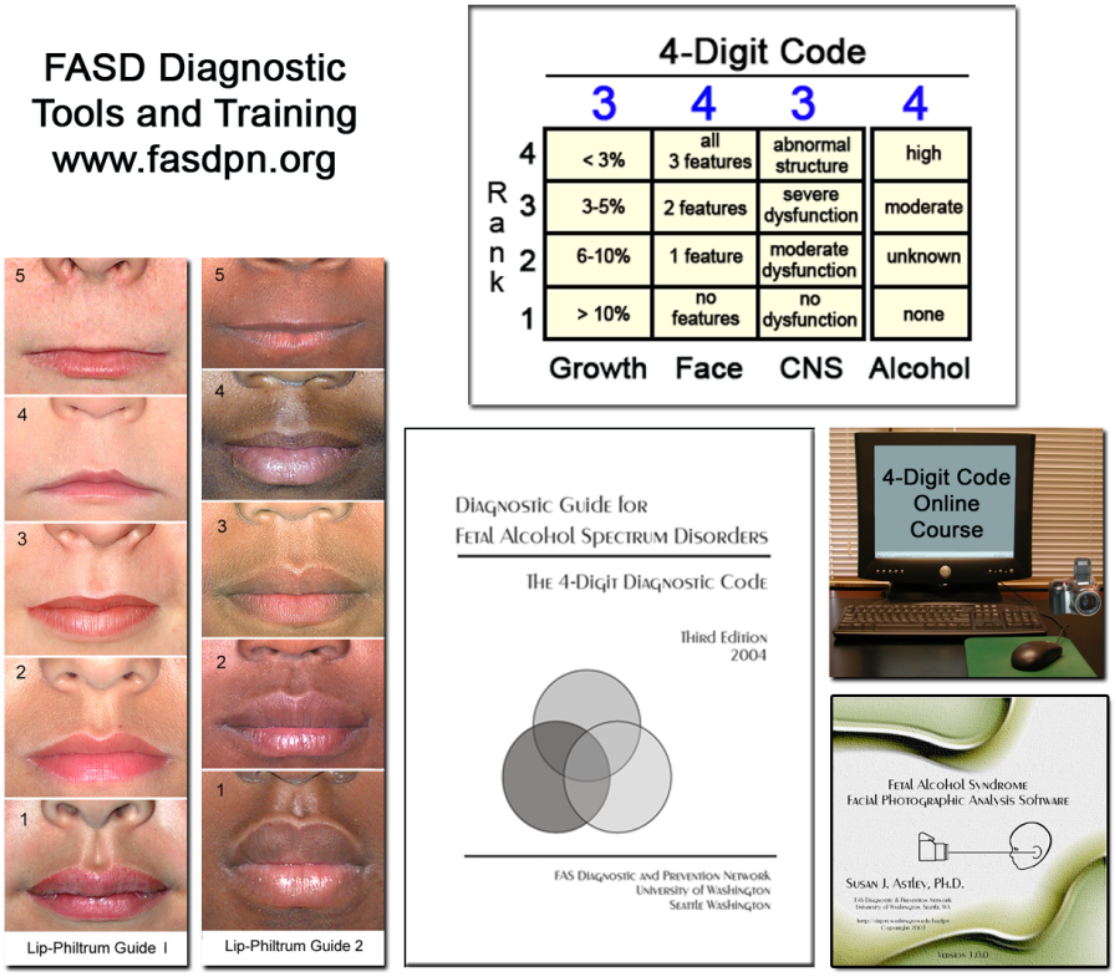

Figure 1. Fetal Alcohol Spectrum Disorders: 4-Digit Diagnostic Code: guide, tools and training.

Key Research Questions

Requisite to the development of diagnostic guidelines is validation of their performance, both before and after their release. Performance should be authenticated through published empirical studies. Measures of performance include accuracy, reproducibility, validity, and practicality.[28] Diagnostic teams should look for the following benchmarks in current FASD diagnostic guidelines:[1,3,28-32]

1. Are the guidelines evidence-based and developed from a broad, representative population-base? The evidence-base should include validation of performance prior to the guideline's release.
2. Do the guidelines endorse an interdisciplinary approach to diagnosis?
3. Are the diagnostic criteria specifically and comprehensively case-defined?
4. Do the diagnostic tools maximize measurement accuracy and precision?
5. The features that characterize FASD (growth, face, CNS, alcohol) are not simply present or absent. Each present along separate, clinically meaningful continua. Are these continua reflected in the guideline's measurement and classification scales?
6. The validity of an FAS diagnosis rests entirely on its unique facial phenotype. Therefore, the sensitivity and specificity of the FAS facial phenotype must be high (>90%) and empirically confirmed. Do the guideline's facial criteria meet these criteria?
7. Do the guidelines identify diagnostic subgroups that are: a) clinically and statistically distinct from one another, b) reflect a continuum of increasing neuropsychological and physical abnormality, and c) span the full continuum of FASD?
8. Does the diagnostic nomenclature assert clinical integrity?
9. The validity of the scales used to measure and classify exposures and outcomes is demonstrated by their ability to detect statistically-significant, physiologically meaningful correlations between physical outcomes, functional outcomes and alcohol exposure levels. With the scales: Does face predict brain? Does neurofunction correlate with neurostructure? Do diagnostic subgroups have unique alcohol-exposure patterns?
10. Are the guidelines readily adoptable into clinical practice? Their practicality should not be at the expense of their accuracy and precision. Training should be expedient, affordable, universally available and competency-based.

Recent Research Results

Below are examples of how the FASD 4-Digit Code meets all 10 benchmarks.

1. *Evidence-based*: The medical records of 1,014 patients (newborn-adult, all races) receiving FASD diagnostic evaluations in the statewide FASDPN were used to develop the 4-Digit Code. Its performance was validated prior to its release through both empirical analysis and

a two-year trial of use by an interdisciplinary team.[15]

2. *Interdisciplinary approach*: The guidelines necessitate the measurement and differential interpretation of physical (growth and dysmorphology) and functional (psychological, language, motor-sensory) outcomes, often in the context of complex social/environmental settings. This requires the expertise of an interdisciplinary team.[25,26]
3. *Case-definitions, measurement tools*: Continuum of exposure and outcome: Case-definitions, measurement tools: All criteria are specifically/operationally case-defined. For example, in contrast to the IOM definition of the FAS facial phenotype ("a characteristic pattern that includes features such as short *palpebral fissure length (PFL)*, flat upper lip, flattened *philtrum* and flat midface"),[1] the 4-Digit Code defines how short, how thin, and how smooth these first three features must be, and provides tools (Lip-Philtrum Guides and FAS Facial Photographic Analysis Software[33]) to accurately measure these features along their full continuum. The 4-Digit Code also recognizes the FAS facial phenotype is not simply present or absent. Its magnitude of expression is measured on a 4-point scale.[15]
4. *Continuum of exposure and outcome*: All FASD features are measured and classified on continuous or ordinal scales. Lips and philtrums are measured on 5-point *Likert scales*. Growth, face, CNS and alcohol are ranked on 4-point scales (Fig. 1). Even the diagnostic subgroups (ND/AE, SE/AE, and FAS/PFAS) reflect three distinct groups with increasing physical/functional impairment.[15,23,26,27,34,35]
5. *Specificity of FAS face*: The Rank 4 FAS facial phenotype is over 95% sensitive and specific to FAS and prenatal alcohol exposure.[2,36,37]
6. *Distinct diagnostic subgroups*: *MRI* /*MRS* /*fMRI* [23,26,27,34,35] have confirmed ND/AE, SE/AE and FAS/PFAS are three clinically distinct, increasingly more severe diagnostic subgroups with unique alcohol exposure patterns. For example, although FAS/PFAS and SE/AE both present with severe dysfunction and disproportionately smaller *caudates*, only FAS/PFAS has the full FAS facial phenotype, disproportionately smaller frontal lobes, significantly lower neurocholine levels, and a significantly higher frequency and duration of alcohol exposure. And although neither SE/AE nor ND/AE present with the full FAS facial phenotype, SE/AE presents with more severe dysfunction, disproportionately smaller caudates and a significantly higher quantity of alcohol exposure. And despite ND/AE's moderate dysfunction, MRI confirms a high prevalence of underlying neurostructural abnormality.

7. *Nomenclature integrity*: The terms SE/AE and ND/AE replace the terms ARND and FAE to accurately document an individual's outcomes and exposure without implying a causal association has been confirmed (or ruled-out) between the two.[15,17,28,29]
8. *Validity*: Published empirical studies[2,15,23,26,27,34-37] document a broad array of physiologically cogent relationships between exposures and outcomes. A few examples: Face predicts brain: IQ and regional brain volumes decrease incrementally and significantly with increasing expression (Ranks 1-4) of the FAS facial phenotype. Neurofunction correlates with neurostructure: The 3-point scale for CNS dysfunction (Rank 1=none, Rank 2=moderate, Rank 3=severe) is significantly associated with decreasing caudate volume.
9. *Readily adoptable into practice*: The guidelines and tools are distributed free or at cost via the web. Training is online, accredited, low-cost and can be completed in a weekend.[38]

Research Gaps

The problems (outlined above) that initially hindered FASD diagnosis have now been overcome with the adoption of rigorous diagnostic guidelines administered by interdisciplinary teams.[2,3,15,23,26-28,34,35,37,39] It is now time to focus research on FASD intervention.[40]

Conclusions

The FASD 4-Digit Diagnostic Code offers an intuitively logical, numeric approach to reporting outcomes and exposure that reflects the true diversity and continuum of disability associated with prenatal alcohol exposure. It also offers substantially greater precision, accuracy and validity than the gestalt method of diagnosis, through the use of quantitative measurement scales, specific case-definitions and an interdisciplinary team approach.

Implications for Parents, Services and Policy

Parents (830 over 13 years) have expressed high satisfaction with the FASDPN interdisciplinary approach to diagnosis using the 4-Digit Code.[26] They report the method was easy to understand and provided them with information they were unable to obtain elsewhere (99% would recommend the clinic to others). The FASDPN model has also earned the respect of service providers statewide. The diagnostic reports provide the detail and direction providers need to qualify children for services. Parents of children with FAS/PFAS, SE/AE and ND/AE confirm being able to access and benefit from recommended interventions.[26] The interdisciplinary model and 4-

Digit Code have been adopted worldwide, often initiated and supported through legislative policy.[26,41-44]

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CANADIAN PALPEBRAL FISSURE LENGTH GROWTH CHARTS REFLECT A GOOD FIT FOR TWO SCHOOL AND FASD CLINIC-BASED U.S. POPULATIONS

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ABSTRACT

Background
Short palpebral fissure lengths (PFL) are one of three facial features that define the unique facial phenotype of fetal alcohol syndrome (FAS). Published PFL growth charts vary greatly in both rate and magnitude of growth, placing their accuracy and validity in question. New PFL growth charts were recently published to reflect a racial/ethnic cross section of Canadian girls and boys 6-16 years of age. PFLs were measured from digital facial photographs using the FAS Facial Photographic Analysis Software.

Objectives
Assess the goodness of fit of two U.S. populations (healthy children and children with prenatal alcohol exposure) when plotted on the Canadian, Hall, and other published PFL charts.

Methods
The PFLs of 106 healthy children and 822 children with prenatal alcohol exposure from Washington State were measured from digital facial photographs using the FAS Facial Photographic Analysis Software. Goodness of fit was assessed graphically and by computation of the mean PFL z-score.

Results
Our predominantly Caucasian, healthy group of children scattered along the mean growth curve on the Canadian charts (mean PFL z-score +0.2), and fell 1.6 SDs below the mean on the Hall chart (mean PFL z-score -1.6). The mean PFL z-score for the children with FAS was 2.4 SDs below the mean on the Canadian charts and 3.9 SDs below the mean on the Hall chart. African Americans were not a good fit.

Conclusion
The Canadian PFL charts were a good fit for our predominantly Caucasian populations of healthy U.S. school-aged children. Children with FAS continued to present with PFLs 2 or more SDs below the mean when plotted on the Canadian PFL charts, supporting the FAS PFL diagnostic criteria used by the FASD 4-Digit Diagnostic Code. Use of PFL charts normed for African Americans is recommended. Updated PFL charts for 0-6 years of age are vital to prevent an artificial over-estimation of short PFLs in this age group.

Key Words: *Fetal alcohol syndrome (FAS); fetal alcohol spectrum disorders (FASD); FASD 4-Digit Diagnostic Code; palpebral fissure length*

Short palpebral fissure length (PFL) is a minor physical anomaly noted in several syndromes including fetal alcohol syndrome (FAS) The PFL is the distance between the endocanthion and exocanthion landmarks (Figure 1). Published charts depicting normal growth of the PFL have been generated from a variety of populations (both healthy and clinical) using a variety of measurement techniques (tape measures, rulers, calipers, photos).[1-9] The size and rate of growth of the PFL vary tremendously across these charts (Figure 2). This has led some to question their accuracy/validity.[10-13] As long ago as 1966, an opthalmalogist named Fox[13] expressed the following concern "literature on the subject (palpebral fissure) is scarce; where it exists no two authorities seem to agree on the size, shape and proportions of the lid fissure".

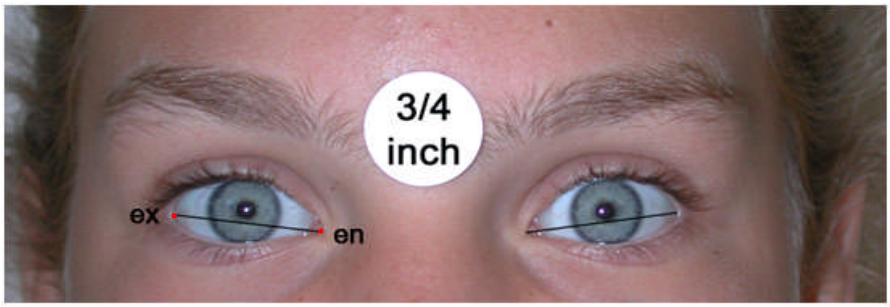


FIG. 1 The palpebral fissure length (PFL) is the distance from the inner corner of the eye (endocanthion landmark) to the outer corner of the eye (exocanthion landmark). The right and left PFLs were measured in this study using the FAS Facial Photographic Analysis Software.[21] A ¾ inch sticker (19.05 mm) is placed between the patient's eyebrows to serve as an internal measure of scale.

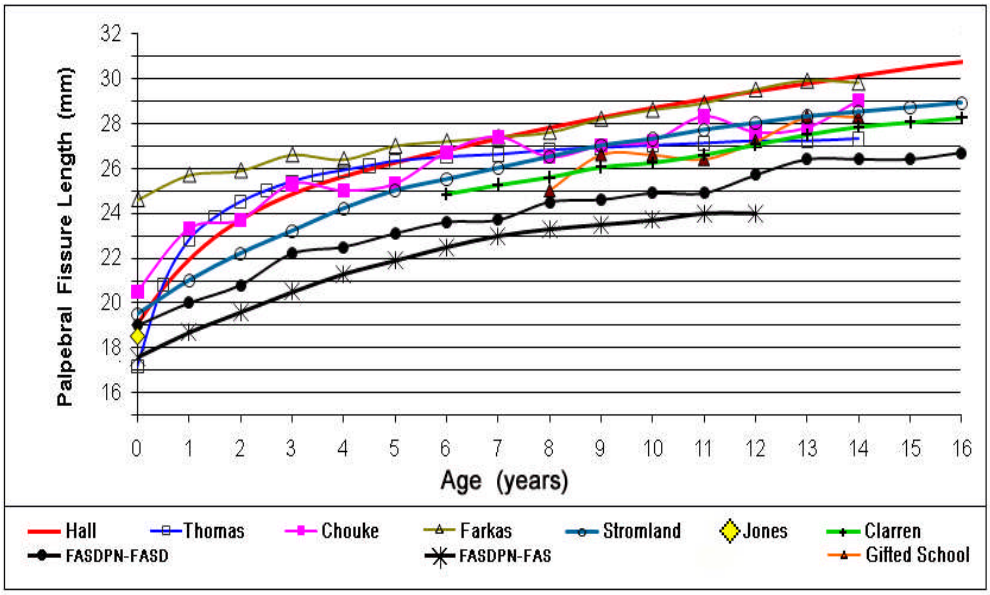


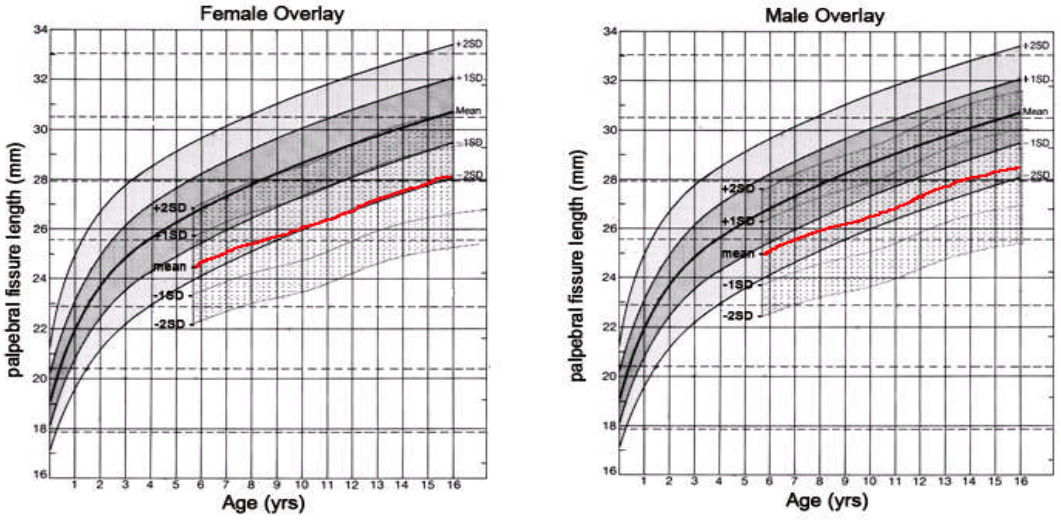
FIG. 2 Comparison of the mean PFL growth curve from published charts depicting normal growth (Hall et al.[5], Thomas et al.[9], Chouke[2], Farkas[3], Stromland et al.[8], Jones et al.[7], and Clarren et al[12]) and selected study samples from Washington State: (children attending a gifted school program (study population 1); and two populations of children diagnosed at the WA State FAS DPN: those with prenatal alcohol exposure (study population 4), and the subset with FAS (study population 3).

When the Washington State FAS Diagnostic & Prevention Network (FAS DPN) first opened in 1993, the Caucasian PFL growth chart constructed by Hall et al[5] was selected for use. The Hall chart is a composite of four previously published charts: Chouke[2]; Farkas[14], Laestadius[15], and Thomas.[9] Chouke[2] used a sliding caliper to measure the PFLs of 258 North American Caucasian patients and medical students, aged 1 week to 35 years of age, from St. Louis Children's Hospital. It is important to note that the purpose of his study was to ascertain the cause of the epicanthal fold, thus all patients showed some degree of the "Mongolian Fold". Farkas[14] used a sliding caliper to measure

the PFLs of 2,326 healthy Caucasian males and females, aged newborn to 25 years of age, residing in Alberta, Ontario, and Quebec, Canada. Thomas[9] derived a mathematical model of PFL growth from 348 North American Caucasian children 29 weeks to 14 years old. The PFLs were obtained from Chouke[2] and Jones et al.[7] Jones et al[7] used a ruler to measure the PFLs of 200 North American Caucasian newborns (32 to 40 weeks gestation). Laestadius[15] measured the innercanthal distance (distance between the right and left endocanthions) and the outer orbital distance (distance between the outermost edges of the bony orbits) of 472 Caucasian individuals, premature to adult, from clinical and school populations. Laestadius did not measure PFL. If one subtracted the innercanthal distance from the outer orbital distance and divided the outcome by two, one could compute the mean distance from the endocanthion to the outer orbital ridge. The distance from the endocanthion to the outer orbital ridge, by definition, is not the PFL. This measure would exceed the PFL by 4 to 5 mm, as depicted in Figure 1 published by Clarren et al[12] Ten years after the publication of the Hall PFL charts, Stromland et al[8] published PFL charts for white, Scandinavian, healthy males (n=291) and females (n-322), 1 month to 18 years of age, using photogammetry. And most recently, in 2010, Clarren et al[12] published PFL charts for a racial/ethnic cross section of Canadian girls (n=1,194) and boys (n=903), 6-16 years of age. PFLs were measured from digital facial photographs using the FAS Facial Photographic Analysis Software.

Over the years, it became apparent that the PFLs of Caucasian patients evaluated in the WA FAS DPN were frequently 2 or more standard deviations (SD) below the mean depicted on the Hall PFL chart. One plausible explanation for this observation could be that the PFL is especially vulnerable to the adverse impact of prenatal alcohol exposure. To test this theory, Dr. Astley measured a small, convenient sample of volunteers (the FAS DPN clinical staff, including herself) to see where they fell on the Hall PFL charts. Surprisingly, most fell two or more SDs below the mean. The individual with the largest PFLs fell 1 SD below the mean. This outcome suggested the Hall PFL chart over-estimated the normal size of a PFL. To further assess the accuracy of the Hall chart, the PFLs of 90 healthy children attending a Washington State elementary school for gifted children were measured with Human Subjects Review Board approval and parental consent in 1999. A gifted school program was selected to minimize risk of adverse outcomes from prenatal alcohol exposure. The average PFL of the 90 predominantly Caucasian children from 6.0 to 16.0 years of age was 1.6 SDs below the mean when plotted on the Hall PFL chart (Figure 3, Table 1). Once again, the Hall PFL charts appeared to over-estimate the normal size of a PFL. This outcome was not unique to the Hall PFL chart. Based on Figure 2, all published PFL charts[2,3,5,.8,.9] appeared to over-estimate the size of the PFL observed in our samples by 1-3 mm (or 4-12%). The magnitude of this over-estimate is clinically concerning, since 1.5 mm is roughly equivalent to 1 SD. Until new, more accurate PFL charts became available, the FAS DPN chose to continue using the Hall PFL chart because even though it appeared to over-estimate the length of a normal palpebral fissure, the rate of growth (slope) depicted in the chart best matched the rate of growth observed across the lifespan in both our clinic and normal populations (Figure 2). Use of a PFL growth chart that matched our rate of growth assured that the PFL would be over-estimated equally across the lifespan, preventing age-dependent diagnostic misclassification. Although the best error is no error at all, the next best option is to select a chart that produces a consistent error, rather than an inconsistent error. If one uses a PFL chart that over-estimates the length of a normal palpebral fissure, the chart will over-estimate the prevalence of short palpebral fissures. This, in turn could lead to a risk of over-diagnosis of FAS. We were aware of this risk, but observed that when a patient presented with all of the features of FAS as defined by the 4-Digit Code (growth deficiency, all three FAS facial features, CNS abnormalities, and alcohol exposure), their PFLs were not just 2 SDs below the mean (as required by the diagnostic guidelines), but were always 3-4 SDs below the mean. It appeared the Hall PFL charts were not leading to an over-diagnosis of FAS in our clinics. It was always our belief that the Hall PFL charts over-estimated the PFL by 1-2 mm. With the creation of the Canadian PFL charts[12], we now have an opportunity to test this hypothesis.

Canadian palpebral fissure length growth charts reflect a good fit for two school and FASD clinic-based U.S. populations



3A **3B**

FIG. 3 Illustration of the contrast between the Canadian[12] and Hall[5] PFL growth charts. The Canadian female (A) and male (B) PFL growth charts (speckled backgrounds), for children 6 to 16 years of age, are overlaid on the Hall PFL growth chart for both genders, 0-16 years of age. The red lines on the overlays reflect the mean PFL growth curve. The mean PFL growth curve (red line Fig. 3A) for Canadian females aligns with the -2.0 SD growth curve on the Hall PFL chart. The mean PFL growth curve (red line Fig. 3B) for Canadian males aligns with the -1.5 SD growth curve on the Hall PFL chart.

TABLE 1 Mean PFL z-scores* for the four study populations when plotted on the Hall[5] and Canadian[12] PFL charts.

Study Population	N	Hall[5] PFL z-score mean (SD)	Canadian[12] PFL z-score mean (SD)	Age range years
1. Healthy School-based				
Both genders	90	-1.59 (0.90)	+0.17 (0.82)	6.0 - 16.0
Girls	42	-1.80 (0.83)	+0.17 (0.87)	6.0 – 16.0
Boys	48	-1.40 (0.93)	+0.18 (0.82)	6.0 – 16.0
2. Healthy MRI Controls				
Both genders	16	-1.66 (0.69)	+0.19 (0.67)	8.3 – 15.8
Girls	8	-1.76 (0.49)	+0.16 (0.84)	8.3 – 14.4
Boys	8	-1.55 (0.87)	+0.22 (0.51)	8.4 – 15.8
3. FAS DPN: FAS				
Both genders	22	-3.86 (0.82)	-2.36 (0.97)	6.2 – 13.8
Girls	11	-4.18 (1.02)	-2.51 (1.22)	6.6 – 13.8
Boys	11	-3.55 (0.40)	-2.21 (0.65)	6.2 – 12.6
4. FAS DPN: prenatal alcohol exposed				
Both genders	822	-2.61 (1.45)	-1.05 (1.46)	6.0 – 16.9
Girls	320	-2.74 (1.52)	-1.04 (1.61)	6.0 – 16.9
Boys	502	-2.54 (1.41)	-1.06 (1.36)	6.0 – 16.9

* A z-score reflects how many standard deviations a data point is from the normal population mean. The mean PFL for a healthy population would be expected to have a mean z-score close to 0.0. The mean PFL for a population with FAS should have a mean z-score at or below -2.0.

METHODS

Primary Objectives

The primary objectives of this study were to:

1. Compare the Canadian[12] and Hall[5] PFL normal growth charts.
   a. Graphically overlay digital images of the two charts to compare the positions of the mean, ±1SD, and ±2SD growth curves.
2. Determine the goodness of fit of a healthy U.S. population on the Canadian[12] and Hall[5] PFL normal growth charts:
   a. Plot the PFLs of 106 healthy U.S. children on the Canadian and Hall PFL normal growth charts to visually assess goodness of fit. A good fit would be depicted by U.S. PFLs scattering along the mean PFL growth curves on the two charts.
   b. Compute PFL z-scores for the 106 healthy U.S. children (using on the population mean and 1-SD levels depicted in the Canadian and Hall PFL normal growth charts) to quantitatively assess goodness of fit. A good fit would be depicted by a mean PFL z-score near zero.
3. Determine how far below the mean a U.S. population of patients with FASD fall on the Canadian[12] and Hall5 normal PFL charts.
   a. Compute the mean PFL z-scores for 1) 822 patients with prenatal alcohol exposure and 2) the subset of 22 with full FAS, using the population mean and 1-SD levels depicted in the Canadian and Hall PFL normal growth. One would expect the mean PFL z-scores for the alcohol exposed group to fall between zero and -2.0. The mean PFL z-score for FAS should be at or below -2.0.
   b. Plot the mean PFL growth curve for the 822 patients with prenatal alcohol exposure and the subset of 22 with full FAS on a composite graph of published mean PFL growth curves to visually compare and contrast.
4. Compare the mean PFL growth curves across several published PFL normal charts.
   a. Plot the mean PFL growth curves for the following published PFL charts[2,3,5,7,8,9,12] and the healthy and FASD populations from our U.S. healthy and alcohol-exposed study samples.
5. Assess the impact of race (specifically: Caucasian versus African American) on PFL.
   a. Compare the mean PFL between Caucasian and African American among the WA FAS DPN populations.

Study Populations

PFLs from four existing U.S. (Washington State) study populations were used in this study. The populations were restricted to those individuals from 6.0 to 16.9 years of age to match the age range portrayed in the Canadian PFL charts. All datasets were collected with Human Subject Review Board approval.

1. Healthy School Population (1999): 90 healthy children (6.0-16.0 years of age) from a Washington State elementary school for gifted children. (47% female, 89% Caucasian, 1% African American). A gifted program was selected to minimize the risk of prenatal alcohol exposure.
2. Healthy MRI Control Study Population (2003): 16 healthy children (8.3-15.8 years of age) enrolled as controls in a University of Washington FASD magnetic resonance study.[16-19] (50% female, 81% Caucasian, 6% African American). Prenatal alcohol exposure was confirmed absent.
3. FAS Clinical Population (1993-2005): 22 individuals (6.2-13.8 years of age) with a 4-Digit Diagnosis of FAS (Diagnostic categories A and B) from the WA State FAS DPN clinical database[20] (50% female, 73% Caucasian, 5% African American).
4. Alcohol-Exposed Clinical Population (1993-2005): All 822 individuals (6.0-16.9 yrs of age) receiving a FASD diagnostic evaluation at the WA State FAS DPN[20] (39% female, 49% Caucasian, 7% African American, 10% FAS/Partial FAS, 33% Static Encephalopathy/Alcohol Exposed, 52% Neurodevelopmental Disorder/Alcohol Exposed). All had confirmed prenatal alcohol exposures.

Acquisition and measurement of digital facial photographs.

All PFLs were measured by one individual (SJA) from digital facial photographs taken by one photographer (SJA) using the FAS Facial Photographic Analysis Software.[21] Briefly, over

the past two decades, standardized digital frontal facial photographs were obtained for the subjects in the four clinical, research, and school-based populations described above. For study population 1 (the school population) only the eyes were photographed to maintain confidentiality. Photographic standardization included no left-to-right rotation of the head, camera lens aligned in the subject's Frankfort horizontal plane (see video animation posted on FAS DPN website), and eyes fully open so the endocanthion and exocanthion landmarks were clearly visible (Figure 1). A ¾ inch (19.05 mm) paper sticker was placed on the forehead between the eyebrows as an internal measure of scale. To measure the PFLs, the digital photos are opened into the FAS Facial Photographic Analysis Software. The User enters the subject's gender, birth date, photo date, and the size of the internal measure of scale (3/4 inch sticker on forehead). The User measures the width of the paper sticker and the lengths of the right and left palpebral fissures in the photos using mouse-controlled distance measuring tools provided in the software. A video demonstration of the FAS Facial Photographic Analysis Software is posted on the FAS DPN website. The software computes the subject's age in years, computes the right and left PFLs in mm, and computes the PFL z-score based on which normal PFL growth charts the User selected (Caucasian[5], or African American[6]).

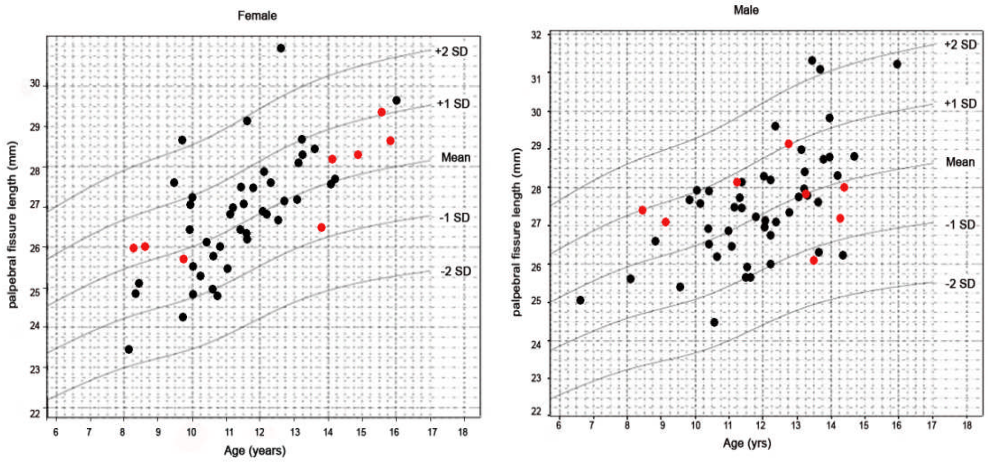
Plotting PFLs of healthy U.S. populations on the Canadian and Hall PFL growth charts.
The PFLs of the two healthy U.S. study populations (study populations 1 and 2) were plotted on the male and female Canadian[12] PFL charts and the Hall[5] PFL chart to visually assess how well the U.S. populations clustered around the mean growth curves (Figures 4 a, b, and c).

Computation of PFL z-scores:
PFL z-scores were computed for each subject based on the means and SDs depicted in the Canadian[12] and Hall[5] PFL charts. A z-score reflects the number of standard deviations (SD) a PFL is above or below the population mean depicted on the normal growth chart for that individual's age. Z-scores provide a quantitative measure of where the four study populations fell on the Canadian and Hall PFL charts. The formula for the PFL z-score is as follows: PFL z-score = ((population mean PFL in mm) – (subject's PFL in mm)) / ((population mean PFL in mm) – (population 1 SD PFL in mm)). For example, if a 10 year old girl had a PFL = 24.0 mm, her PFL z-score calculated based on the Canadian PFL chart for girls would be ((26.03 – 24.0)/(26.03-24.76)) = -1.6. In other words, the girl's PFL is 1.6 SDs below the mean for a 10 year old girl as depicted on the Canadian PFL chart.

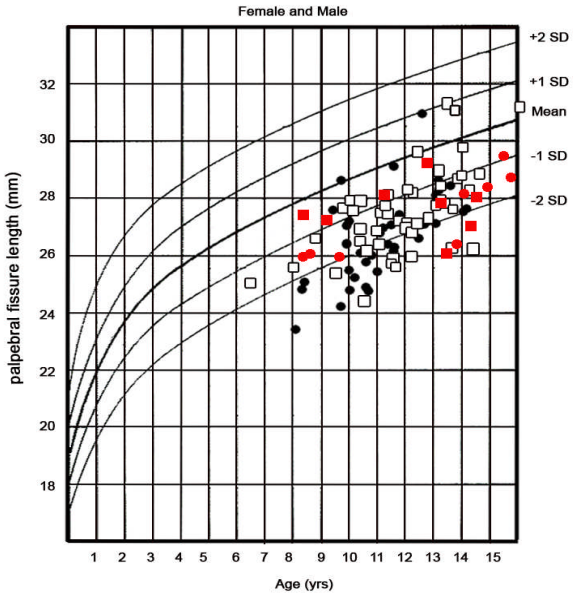
PFL z-scores were computed for each subject based on the population means and SDs depicted in both the Canadian[12] and Hall[5] normal PFL growth charts. To generate the z-scores, the mean and 1 SD lines for the Canadian and Hall PFL charts were digitally traced to generate x,y coordinates along the full length of the growth curves. These x,y coordinates were then used to generate 6th order polynomial best-fit formulas of each line. The formula's predicted the lines with R-squares greater than 0.9999999 (reflecting a perfect fit). These formulas were also used to create a PFL z-score calculator for the Canadian and Hall PFL growth charts posted on the FAS DPN website.

Overlay of Canadian and Hall PFL charts.
Adobe Photoshop CS2[22] was used to overlay captured digital images of the Canadian and Hall PFL charts (Figure 3). This provided a visual comparison of the contrasts in the mean, $\pm$1 SD, and $\pm$2 SD growth curves for individuals 6-16 years of age.

Statistical Analyses
SPSS 14.0[23] was used for all statistical analyses. Chi-square tests and t-tests were used to compare proportions and mean between two groups, respectively. Two-tailed p-values < 0.05 were interpreted as statistically significant.



4A **4B**



4C

FIG. 4 Scatter plots illustrating the goodness of fit of our two healthy U.S. study populations (study populations 1 and 2) on the Canadian[12] and Hall[5] PFL charts. **A**) Canadian female PFL growth chart with the females from the healthy school population (black circles) and healthy MRI control group (red circles) plotted. **B**) Canadian male PFL growth chart with the males from the healthy school population (black circles) and healthy MRI control group (red circles) plotted. **C**) Hall PFL chart for males and females combined with the healthy school population (females: black circles, males black outlined squares) and the healthy MRI control group (females: red circles, males red squares) plotted. Plots A and B reflect a good fit (mean PFL z-scores range from +0.17 to +0.19). Plot C reflects a poor fit (mean PFL z-score = -1.6). These healthy groups of children are depicted on the Hall PFL chart as having PFLs on average 1.6 SDs below the mean (reflecting a poor fit). These same children are depicted as having PFLs on average 0.2 SDs above the mean when plotted on the Canadian PFL charts (reflecting a good fit).

RESULTS

Objective 1. Graphic comparison of Canadian and Hall PFL normal growth charts.
When the Canadian PFL charts are overlaid on the Hall PFL chart, the mean PFL growth curves for Canadian males and females fall 1.5 and 2.0 SDs below the mean, respectively on the Hall PFL growth chart (Figure 3).

Objective 2. Goodness of fit of the healthy U.S. groups on the Canadian and Hall PFL normal growth charts.
The mean PFL of the 106 predominantly Caucasian, healthy U.S. children (90 school-based children and 16 healthy children enrolled as unexposed controls in a MRI study) scatter along the mean PFL growth curve on the Canadian PFL charts (Figures 4A and B). The mean PFL z-scores for the school and MRI study groups were +0.17 and +0.19 respectively (Table 1). Both the scatter plots and mean z-scores are reflective of a very good fit with the Canadian PFL charts. In contrast, these same children scatter, on average, 1.6 SDs below the mean PFL growth curve on the Hall PFL chart (Figure 4C, Table 1) demonstrating a poor fit. The Canadian PFL charts identify these children as having normal PFLs. The Hall PFL charts identify these children as having PFLs that are, on average, 1.6 standard deviations below normal.

Objective 3. Goodness of fit of the U.S. group with FASD on the Canadian and Hall PFL normal growth charts.
The mean PFL z-score for the 22 children diagnosed with full FAS from the WA FAS DPN clinics was 2.4 SDs below the mean on the Canadian PFL charts and 3.9 SDs below the mean on the Hall PFL charts (Table 1, Figure 2). These outcomes document the PFL for a child with FAS continues to fall 2 or more SDs below the mean when the Canadian PFL charts are used. The mean PFL z-score for the larger population of children with prenatal alcohol exposure was 1.1 SDs below the mean on the Canadian PFL charts and 2.6 SDs below the mean on the Hall PFL charts (Table 1, Figure 2). As hypothesized above, when the clinical population is expanded to include all children with prenatal alcohol exposure (not just the subset with FAS), the mean PFL z-score would still fall below the population mean, but not as far below the mean as the subgroup with full FAS. Twenty-five percent of the children with prenatal alcohol exposure had PFLs two or more SDs below the mean on the Canadian PFL charts. Sixty-eight percent of these children had PFLs two or more SDs below the mean on the Hall PFL chart.

Objective 4. Graphic comparison of the mean PFL growth curves across published PFL normal growth charts.
The mean PFL growth curves vary considerably in magnitude and slope across the published PFL normal growth charts[2,3,5,9,8,12] (Figure 2). All present with mean PFLs 0.5 to 2.0 mm greater than that depicted in the Canadian PFL charts. The mean PFL growth curves for the WA State FAS DPN patient population (all FASD and the subset with FAS) have the same rate of growth depicted in the Canadian PFL growth curve, but fall 1 and 2 SDs below the mean Canadian PFL growth curve respectively, as expected.

The greatest variability across the mean PFL growth curves occurs among children under 6 years of age. The rate of growth in the Thomas[9], Hall[5], and Chouke[2] charts, from birth to 4 years of age, is substantially faster than that depicted in the Farkas[3] and Stromland[8] charts. It is important to note that the Hall[5] chart is a composite of Thomas[9], Chouke[2], Farkas[15], and Jones.[7] This rate of growth is not observed in the FAS DPN clinical sample.

Objective 5. Assess the impact of race (specifically Caucasian versus African American) on PFL.
Of the 822 patients with prenatal alcohol exposure from the FAS DPN clinic between 6.0-16.9 years of age, 400 were Caucasian and 54 were African American. These two groups did not differ significantly in mean age, gender, or FASD diagnostic classification. The mean PFL for the African Americans (26.5 mm, 2.0 SD) was 1.5 mm longer than the mean PFL of the Caucasians (25.0 mm, 2.1 SD) ($t = 5.0$, $p < 0.001$) (Figure 5). A 1.5 mm difference is equivalent to 1 SD on the Canadian PFL chart. In other words, if these two racial groups were plotted on the Canadian male and female PFL charts, the mean PFL z-score for the African American group (-0.1, 1.3 SD) would be 1 SD larger than the mean PFL z-score for the Caucasian group (-1.2, 1.4 SD) ($t = 6.0$, $p < 0.001$). Not only is the African American group 1 SD higher on the Canadian PFL chart, but they fall along the mean PFL growth curve

(reflecting normal growth). One would expect an alcohol-exposed group to fall below the mean (like the Caucasian alcohol-exposed group does). There were not a sufficient number of African Americans in our two healthy study populations (populations 1 and 2) to accurately compare PFLs between healthy, unexposed African Americans and Caucasians. There were, however, 105 Caucasian children and 7 African American children evaluated in the FAS DPN clinics whose suspected prenatal alcohol exposures could not be confirmed. The mean PFL for these 7 African Americans (26.2 mm, 1.9 SD) was also 1.6 mm longer than the mean PFL of the 105 Caucasians (24.6 mm, 2.2 SD) ($t = 1.9$, $p = 0.05$).

DISCUSSION

The Canadian PFLs charts[12] provide a much needed update in normal PFL growth from 6.0 to 16.9 years of age across a large, healthy, school-based, racially diverse sample. The current study demonstrates the Canadian PFL norms are a good fit for the PFLs we observed in two predominantly Caucasian, healthy, U.S. (Washington State) school and population-based samples of children. As a result, we have posted a free PFL z-score calculator on our FAS DPN website that will allow clinics to compute a patient's PFL z-score (based on the means and SDs depicted in the Canadian PFL charts) by entering the patient's age, gender, and PFL. We will also include the Canadian PFL charts as one of several PFL growth charts Users may select to use in the next version of the FAS Facial Photographic Analysis Software. The Canadian PFL norms also performed as we would have anticipated for our large, racially diverse, alcohol-exposed population evaluated in the WA State FASD diagnostic clinics. Children with FAS continued to present with PFLs 2 or more SDs below the mean when plotted on the Canadian PFL charts, supporting the FAS PFL diagnostic criteria (PFL 2 or more SDs below the mean) used by the FASD 4-Digit Diagnostic Code.[10] When the clinical population was expanded to include all children with prenatal alcohol exposure (not just the subset with FAS), the mean PFL z-score (-1.0) still fell below the population mean, but not as far below the mean as the subgroup with full FAS. The only subgroup that did not appear to be a good fit was our African American group.

It is well established in the published literature that African American's have significantly longer PFLs than Caucasians.[1,3,4] African Americans in our FASD clinical population had PFLs that were on average 1.5 mm longer (or 1 SD higher on the Canadian PFL growth charts) than Caucasians, across the lifespan (Figure 5). This magnitude of difference was both clinically and statistically significant, and consistent with the magnitude of difference reported for healthy populations of African Americans and Caucasians.[1,3,4] Starting at birth, Fuchs et al[4] reported the PFL was 1.5 mm longer among African American term neonates (20.0 mm, 2.0 SD) compared to Caucasian neonates (18.5mm, 1.3 SD) (7). Among adults, Barretto et al[1] reported the mean PFLs for African American women and men were 31.5 mm and 32.3 mm, respectively. These measures are on average 2.4 mm longer than PFLs for Caucasian women (29.4 mm) and men (29.5 mm). Farkas[3] reported the mean PFLs for African American adult women and men were 32.3 mm and 32.9 mm, respectively. These measures were on average 1.7 mm longer than the mean PFLs for Caucasian women (30.7 mm) and men (31.3 mm). Although the Canadian PFL charts are based on a racially diverse sample, the proportion of African Americans (2.5%) would not be sufficient to overcome this magnitude of difference in PFL between Caucasians and African Americans. It is well understood that norms based on multiracial groups will marginally over or under estimate the growth of individuals who are indigenously at the upper and lower boundaries of the physical spectrum. Clarren et al[12] created separate male and female PFL charts because of their 0.5 mm difference in PFL. The magnitude of difference between African American and Caucasian PFLs is 1.5 to 2.4 mm. This magnitude of difference warrants the use of PFL charts normed to African Americans. African American PFL normal growth charts exist[1,3,4,6], but they too would undoubtedly benefit from an update. The FAS DPN uses the Iosub et al[6] African American PFL charts for African American patients because they provide norms for children. A 10 year old African American boy with a PFL of 26.5 mm would fall directly on the mean using the Canadian multiracial chart for boys (PFL z-score 0.0), 1.6 SDs below the mean on the Hall Caucasian PFL chart, and 2.1 SDs below the mean on the Iosub[6] African American PFL charts.

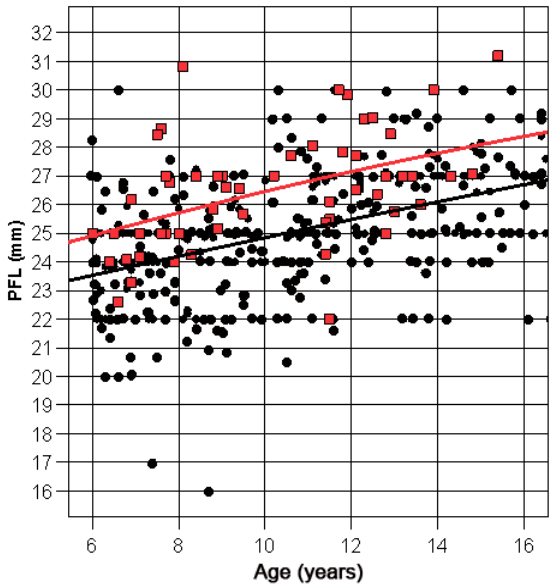


FIG. 5. Among the patients with prenatal alcohol exposure (study population 4), African Americans (red squares, red best linear-fit line) had significantly larger PFLs (mean = 26.5 mm, 2.0 mm SD) than the Caucasians (black circles, black best linear-fit line) (mean = 25.0mm, 2.1 mm SD). Age, gender, and FASD diagnostic classification were comparable between the two groups.

The Canadian PFL charts are a valuable clinical resource for use with patients 6 years of age and older. The absence of updated PFL charts for children under six years of age, however, poses quite a dilemma, especially in FASD diagnostic clinics where accurate interpretation of the PFL is critical to the accurate diagnosis of FAS. If a clinic uses the Canadian PFL charts for children 6 years of age and older, they will have to use one of the other currently published PFL charts for children under 6 years of age.

This will result in an abrupt increase in PFL as one transitions from the Canadian charts for older children to other published PFL charts for younger children (Figure 5). This, in turn, will create what appears to be a higher prevalence of short PFLs among children under age 6 versus over age 6. To illustrate this-the mean PFL for a 6-year-old boy is 25 mm on the Canadian[12] chart. The mean PFL for a 5.9-year-old boy leaps to 26.5 mm to 27.2 mm on the Thomas et al[9], Hall et al[5], and Farkas[3] charts. To further illustrate-a PFL of 25 mm reflects the mean PFL for a 6-year-old boy on the Canadian[12] charts. This same PFL reflects the mean PFL for a 5-year-old on the Stromland et al[8] chart, a 4-year-old on the Chouke[2] chart, a 3-year-old on the Hall et al[5] chart, a 2.3-year-old on the Thomas et al[9] chart, and a 6-month-old on the Farkas[3] chart. Updated PFL growth charts for children birth to 6 years of age are needed immediately. The U.S. National Children's Study[24] could serve as an excellent source of data to generate these norms. The National Children's Study is a prospective longitudinal observational study that will examine the effects of the environment and genetics on the growth, development, and health of thousands of children across a representative U.S. sample, following them from before birth until age 21 years.

Acknowledgements

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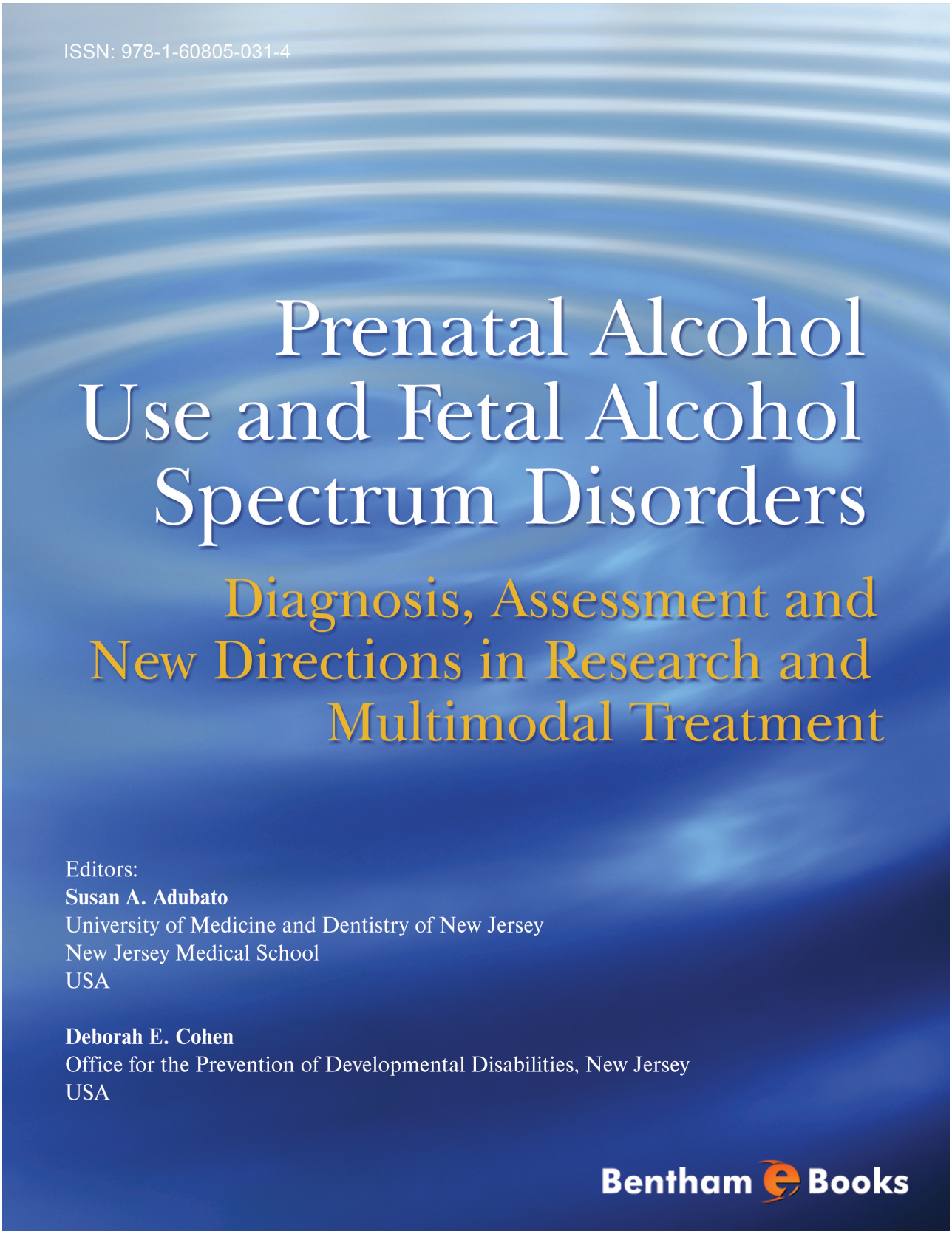
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CHAPTER 1

Diagnosing Fetal Alcohol Spectrum Disorders (FASD)

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While we try to teach our children about life, our children teach us what life is all about

Angela Schwindt

Abstract: Fetal Alcohol Syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. Almost four decades have passed since the term FAS was first coined. The condition is now recognized as a spectrum of disorders: Fetal Alcohol Spectrum Disorders (FASD). Substantial progress has been made in developing specific criteria for delineating diagnoses under the umbrella of FASD. In the 14 years since the publication of the seminal report on FAS by the Institute of Medicine in 1996, clear consensus has been reached on two fundamental issues: 1) an FASD diagnostic evaluation is best conducted by a team of professionals from multiple disciplines (medicine, psychology, speech-language, occupational therapy) and 2) the team should use rigorously case-defined and validated FASD diagnostic guidelines. This chapter will provide a brief overview of the discovery of FASD, diagnostic challenges, how diagnostic guidelines and clinical models have evolved over time to address these challenges, and how new technology may influence the future of FASD diagnosis.

INTRODUCTION

What is FASD?

Fetal Alcohol Syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. The definition of FAS has changed little since the 1970's when the condition was first described and refined [1-5]. The condition has been broadly characterized by prenatal and/or postnatal growth deficiency, a unique cluster of minor facial anomalies, and central nervous system (CNS) abnormalities. FAS is the leading known preventable cause of intellectual disabilities in the Western World [6]. The prevalence of FAS is estimated to be 1 to 3 per 1,000 live births [1] in the general population, but has been documented to be as high as 10 to 15 per 1,000 in some higher-risk populations such as children residing in foster care [7,8].

The physical, cognitive, and behavioral deficits observed among individuals with prenatal alcohol exposure are not dichotomous, that is either normal or clearly abnormal. Rather, the outcomes, and the prenatal alcohol exposure, all range along separate continua from normal to clearly abnormal and distinctive [9-12]. This full range of outcomes observed among individuals with prenatal alcohol exposure has come to be called Fetal Alcohol Spectrum Disorders (FASD). Diagnoses like FAS, Partial FAS (PFAS), and Alcohol-Related Neurodevelopmental Disorder (ARND) fall under the umbrella of FASD.

The Diagnostic Challenge

FASD can present a daunting, but not insurmountable challenge for diagnosis. Individuals with prenatal alcohol exposure present with a wide range of outcomes, most of which are not specific to prenatal alcohol exposure and often manifest differently across the lifespan. Professionals from multiple disciplines (medicine, psychology, speech-language pathology, occupational therapy, etc.) are needed to assess and interpret accurately the broad array of outcomes that define the diagnoses. The pattern and severity of outcomes are dependent on the timing, frequency, and quantity of alcohol exposure (which is rarely known with any level of accuracy), and is frequently confounded by other adverse prenatal and postnatal exposures and events.

In the absence of objective, accurate, and reproducible methods for measuring and recording the severity of exposures and outcomes in individual patients, diagnoses have varied widely from clinic to clinic [1,13-16]. From a clinical perspective, diagnostic misclassification leads to inappropriate patient care, increased risk for secondary

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Susan Adubato and Deborah Cohen (Eds)

disabilities [17], and missed opportunities for primary prevention [18]. From a public health perspective, diagnostic misclassification leads to inaccurate estimates of incidence and prevalence [1,14,16,19]. Inaccurate estimates thwart efforts to allocate sufficient social, educational, and health care services to this high-risk population, and preclude accurate assessment of primary prevention intervention efforts. From a clinical research perspective, diagnostic misclassification reduces the power to identify clinically meaningful contrasts between FAS and control groups and between FASD clinical subgroups like FAS and ARND [9,14,20]. Non-standardized diagnostic methods also thwart valid efforts to compare outcomes between research studies [9,10, 21].

DISCOVERY OF FETAL ALCOHOL SYNDROME

Reference to the harmful effects of maternal drinking on infant outcome date back to biblical times (Behold, thou shalt conceive, and bear a son; and now drink no wine or strong drink…Judges 13:7) [22], with several remarkably comprehensive descriptions by physician groups in the 1700s and 1800s [23-25]. But several hundred years would go by before another entry would be made to the medical literature. In 1968 Lemoine and colleagues from France published an article describing 147 patients [26]. In 1970, unaware of the Lemoine publication, Ulleland and colleagues from Seattle, Washington published similar observations describing a small group of alcohol-exposed infants admitted to several high-risk maternal-child health clinics at the University of Washington [27,28]. Dr. Ulleland's findings were accepted for presentation at the American Pediatric Society-Society for Pediatric Research meeting, held in Atlantic City New Jersey in 1970 [27]. Through a presentation to the University of Washington pediatric faculty, David Smith, M.D., a dysmorphologist, became interested in Dr. Ulleland's research. This would eventually lead to a collaborative publication in 1973 describing the pattern of outcome associated with prenatal alcohol exposure [29] and the publication that coined the term FAS [2].

Initial FAS Diagnostic Guidelines (1973-89)

Progress in refining the FAS diagnosis can be traced by reviewing Clarren and Smith [4], who summarized the available clinical reports from 1973 to 1976, and the reports from the fetal alcohol workshops of the Research Society of Alcoholism in 1980 and 1989 [3,5].

IOM FAS Diagnostic Guidelines (1996)

In recognition of the seriousness of FAS for the individual and society, the U.S. Congress mandated (in Section 705 of Public Law 102-321, the ADAMHA Reorganization Act) the Institute of Medicine (IOM) of the National Academy of Sciences to conduct a study of FAS and related birth defects. A seminal report was published in 1996 covering the full spectrum of issues from prevalence, diagnosis, prevention, to treatment [1]. A chapter entitled "Diagnosis and Clinical Evaluation of FAS" was included. The committee was charged with evaluating existing diagnostic criteria and formulating the best possible diagnostic guidelines reflective of current knowledge. The IOM diagnostic guidelines for FASD are presented in their entirety across Tables 1-4, as they represent an important baseline from which current guidelines evolved. The IOM committee recognized the following issues as central to delineating FASD:

1. Should a documented history of exposure to alcohol be required for a diagnosis of FAS?
2. Which physical features should be used to define the disorder?
3. Can behavioral or cognitive features be used to define the disorder?
4. Is there a role for ancillary measures (e.g., magnetic resonance imaging [MRI] in making the diagnosis?
5. Can criteria be designed to be used across the lifespan?
6. What is the relationship of so-called fetal alcohol effects to fetal alcohol syndrome?

These issues will be discussed later in this chapter as they relate to both the IOM guidelines and current guidelines.

While the IOM guidelines reflected an important advancement in FASD diagnosis: 1) the IOM committee felt "a medical diagnosis of FAS remained the purview of dysmorphologists and clinical geneticists" (page 79), and 2) the guidelines remained intentionally broad and conceptual (e.g., gestalt) rather than specific and operational (e.g., case-defined) [1].

Table 1. FAS diagnostic criteria: Comparison across the five most current FAS/D diagnostic guidelines.

	4-Digit Code (2004)[38]	CDC (2004) [36]	Canadian (2005) [37]	Hoyme (2005)[19]	IOM (1996)[1]
Growth	Prenatal and/or postnatal height or weight ≤ 10th percentile (Growth Ranks 2-4)	Prenatal and/or postnatal height or weight ≤ 10th percentile (Growth Ranks 2-4)	At least 1 of the following: • Prenatal and/or postnatal height or weight ≤ 10th percentile • Weight-to-height ratio (≤10th percentile) (Growth Ranks 2-4)	Prenatal and/or postnatal height or weight ≤ 10th percentile (Growth Ranks 2-4)	At least 1 of the following: • Low birth weight • Low weight for height • Decelerating weight (Growth Ranks 1-4)
Face	All 3 of the following at any age: • PFL ≤ 3rd percentile • Smooth philtrum Rank 4 or 5 • Thin upper lip Rank 4 or 5 (Face Rank 4)	All 3 of the following: • PFL ≤ 10th percentile • Smooth philtrum Rank 4 or 5 • Thin upper lip Rank 4 or 5 (Face Ranks 3-4)	All 3 of the following at any age: • PFL ≤ 3rd percentile • Smooth philtrum Rank 4 or 5 • Thin upper lip Rank 4 or 5 (Face Rank 4)	2 or more of the following: • PFL ≤ 10th percentile • Smooth philtrum Rank 4 or 5 • Thin upper lip Rank 4 or 5 (Face Ranks 2-4)	Characteristic pattern that includes features such as short PFL, flat upper lip, flattened philtrum, and flat midface. (Face Ranks 1-4)
CNS	At least 1 of the following: • Structural/Neurological: (e.g., OFC ≤ 3rd percentile, abnormal structure, seizure disorder, hard signs) • Severe Dysfunction: (3 or more domains[a] of function with impairment 2 or more SDs below the mean) (CNS Rank 3 and/or 4)	At least 1 of the following: • Structural/Neurological: (e.g., OFC ≤ 10th percentile, abnormal structure, seizure disorder, hard/soft signs) • Dysfunction[b]: ○ 3 or more domains of function with impairment 1 or more SDs below the mean ○ Global deficit (2 or more SDs below the mean) (CNS Ranks 2-4)	At least 3 of the following Structure/Neurological/ Functional domains with impairment[c]: • Hard/soft signs, structure, cognition, communication, academic achievement, memory, executive functioning, abstract reasoning, ADD, adaptive behavior, social skills, or communication (CNS Ranks 3 and/or 4)	At least 1 of the following: • Structural ○ OFC ≤ 10th percentile ○ Abnormal structure (CNS Rank 1 or 4)	At least 1 of the following: • Structural/Neurological: ○ Decreased cranial size at birth ○ Abnormal structure (e.g., microcephaly, partial/complete agenesis of the corpus callosum, cerebellar hypoplasia) ○ Neurological hard/soft signs (CNS Rank 4?)
Alcohol	Confirmed or Unknown (Alcohol Ranks 2,3 or 4)	Confirmed or Unknown (Alcohol Ranks 2,3 or 4)	Confirmed or Unknown (Alcohol Ranks 2,3 or 4)	Confirmed-excessive or Unknown (Alcohol Ranks 2 or 4)	Confirmed-excessive or Unknown (Alcohol Ranks 2 or 4)

a. 4-Digit Code: Domains may include, but are not limited to: executive function, memory, cognition, social/adaptive skills, academic achievement, language, motor, attention, or activity level.

b. CDC: Performance substantially below that expected for an individual's age, schooling, or circumstances, as evidenced by: 1. Global cognitive or intellectual deficits representing multiple domains of deficit (or significant developmental delay in younger children) with performance below the 3rd percentile (2 standard deviations below the mean for standardized testing) or 2. Functional deficits below the 16th percentile (1 standard deviation below the mean for standardized testing) in at least three of the following domains: a) cognitive or developmental deficits or discrepancies b) executive functioning deficits c) motor functioning delays d) problems with attention or hyperactivity e) social skills f) other, such as sensory problems, pragmatic language problems, memory deficits, etc.

c. Canadian: Impairment indicates scores ≥ 2 SDs below the mean, discrepancies of 1.5-2 SDs among subtests, or ≥ 1 SD discrepancy between subdomains.

The equivalent 4-Digit Ranks for Growth, Face, CNS and Alcohol are inserted in red font to facilitate comparison across the guidelines.

FASD diagnosis has now advanced beyond the 1996 IOM FASD diagnostic guidelines. While areas of debate still exist, the field has reached consensus on two fundamental issues: 1) an FASD diagnostic evaluation is best conducted by an interdisciplinary team of professionals, and 2) the team should use rigorously case-defined and validated FASD diagnostic guidelines.

Interdisciplinary Diagnostic Approach

The University of Washington FAS Diagnostic & Prevention Network (FAS DPN) first introduced an interdisciplinary approach to FASD diagnosis through a CDC-sponsored FAS prevention project conducted in 1992-97 [18,30-32]. Because of the complexity and broad array of outcomes observed in individuals with prenatal alcohol exposure, an interdisciplinary team is essential for an accurate and comprehensive diagnosis and treatment plan. An interdisciplinary FASD diagnostic team typically includes a medical doctor, psychologist, speech language pathologist, occupational therapist, social worker, and family advocate. Other members of the interdisciplinary team may include, but are not limited to, psychiatrists, neuropsychologists, geneticists, public health nurses, and mental health specialists.

Interdisciplinary models will necessarily vary to accommodate site-specific factors like funding, location (rural versus urban), access to services, target population, etc. The model used by the University of Washington FAS DPN diagnostic clinic targets both a general population and a high-risk foster care population. Individuals from the general population (birth to adult) are referred to the clinic by a broad array of community professionals (medical, educational, social-service, justice). In addition, all children who screen positive for the full FAS facial phenotype from the FAS DPN-Foster Care Passport Program FAS screening program [7,8] are also referred to the clinic.

The patient population served by the FAS DPN has expressed strong preference for an evaluation that can be completed in a single visit. Thus, two patients are evaluated per day, one in the morning and one in the afternoon. The interdisciplinary team includes a pediatrician, two psychologists, a speech-language pathologist, an occupational therapist, a social worker, and a family advocate. Prior to an evaluation, previous medical, school, and social records are collected by the clinic coordinator and reviewed by the lead psychologist. On the day of the evaluation, the lead psychologist presents the case to the team. The child is then assessed by the second psychologist, speech language pathologist, and occupational therapist while the caregivers are interviewed by the pediatrician and lead psychologist. Upon completion of the interview, the pediatrician conducts a physical exam of the patient. The team reconvenes to derive the FASD 4-Digit Code and compose an intervention plan. The team shares the diagnostic results and intervention plan with the family at the end of the 4-hour appointment. A single comprehensive report documenting the diagnostic outcome, all data used to derive the diagnostic outcome, and intervention recommendations are submitted to the patient's medical record.

A more detailed description of the interdisciplinary diagnostic approach used by the University of Washington FAS DPN is presented in Clarren et al., [32]. A short video of an interdisciplinary diagnostic team conducting an FASD diagnostic evaluation can be viewed by clicking on http://depts.washington.edu/fasdpn/htmls/diagteamvideo.htm (Fig. 1)

Figure. 1: This video segment portrays an interdisciplinary team conducting an FASD diagnostic evaluation using the FASD 4-Digit Code. The video is a live recording of an actual FASD diagnostic evaluation. The patient is an adolescent adopted from Russia. The interdisciplinary team includes a pediatrician, two psychologists, a speech-language pathologist, an occupational therapist, a social worker, a family advocate, and a public health professional. The child will receive a 4-Digit Code of 4442 (FAS / Alcohol Exposure Unknown). The team conducted a 2-hour interview with the adoptive parents and a 2-hour evaluation of the child. The team has already derived the first two digits of the 4-Digit Code (the Growth and Face Ranks). This segment portrays the team's derivation of the last two digits of the 4-Digit Code (the CNS and Alcohol Ranks). The team will also document all other prenatal and postnatal risk factors that may have contributed to the child's outcomes. This video segment is one of several presented in the FASD 4-Digit Diagnostic Code Online Course offered at the FAS DPN at the University of Washington.[33] Copyright: Susan Astley, University of Washington, Seattle, WA

Current FAS/D Guidelines (1997 2005)

Four FAS/D diagnostic guidelines have been published since the IOM Guidelines in 1996 [1]: the FASD 4-Digit Code in March 1997 [34,35]; the CDC FAS guidelines in July 2004 [36]; the Hoyme FASD guidelines in January 2005 [19], and the Canadian FASD guidelines in March 2005 [37]. The 4-Digit Code was subsequently updated in January, 1999 [34] and November 2004 [38]. All four guidelines are in current use. This is not to imply the 1996

IOM guidelines are not in use. But each of the four new guidelines purports to have been created to replace or augment the 1996 IOM guidelines.

Table 2: Partial FAS diagnostic criteria. Comparison across the five most current FAS/D diagnostic guidelines.

	4-Digit Code (1997-2004)[38]	CDC[a] (2004) [36]	Canadian (2005)[37]	Hoyme (2005)[19]	IOM (1996)[1]
Growth	Prenatal or postnatal height or weight ≤ 10th percentile (Growth Ranks 1-4)	--	No growth deficiency (Growth Rank 1)	Prenatal and/or postnatal height or weight ≤ 10th percentile (Growth Ranks 2-4)	At least 1 of the following: • Low birth weight • Low weight for height • Decelerating weight (Growth Ranks 1-4)
Face	All 3 of the following at any age: • PFL ≤ 3rd percentile • Smooth philtrum Rank 4 or 5 • Thin upper lip Rank 4 or 5 (Face Ranks 3 or 4)*	--	2 of the following at any age: • PFL ≤ 3rd percentile • Smooth philtrum Rank 4 or 5 • Thin upper lip Rank 4 or 5 (Face Ranks 2 or 3)	2 or more of the following: • PFL ≤ 10th percentile • Smooth philtrum Rank 4 or 5 • Thin upper lip Rank 4 or 5 (Face Ranks 2-4)	Some components of the pattern of FAS characteristic facial anomalies. (Face Ranks 1-4)
CNS	At least 1 of the following: • Structural/Neurological: (e.g., OFC ≤ 3rd percentile, abnormal structure, seizure disorder, hard signs) • Severe Dysfunction: (3 or more domains[b] of function with impairment 2 or more SDs below the mean) (CNS Rank 3 and/or 4)	--	At least 3 of the following Structure/Neurological/Functional domains with significant impairment[c]: • Hard/soft signs, structure, cognition, communication, academic achievement, memory, executive functioning, abstract reasoning, ADD, adaptive behavior, social skills, or communication (CNS Rank 3 and/or 4)	At least 1 of the following: • Structural ○ OFC ≤ 10th percentile ○ Abnormal structure • Dysfunction ○ Complex pattern[d] of behavior / cognitive abnormalities (CNS Ranks 1-4)	At least 1 of the following: • Structural/Neurological : ○ Decreased cranial size at birth ○ Abnormal structure ○ Hard/soft signs • Dysfunction ○ Complex pattern[e] of behavior / cognitive abnormalities (CNS Ranks 2-4)
Additional Criteria	PFAS requires the CNS and Alcohol criteria to be met and allows the Growth and/or the Face criteria to be relaxed just slightly. • *One facial feature may be relaxed as follows: (PFL ≤ 1 SD, or Philtrum Rank 3, or Lip Rank 3) or • Growth can be relaxed to normal.	--	None	PFAS requires the Face and Alcohol criteria to be met and only one of the following additional criteria : • Growth • CNS Structural • CNS dysfunction	PFAS requires the Face and Alcohol criteria to be met and only one of the following additional criteria : • Growth • CNS Structural / Neurological • CNS dysfunction
Alcohol	Confirmed (Alcohol Ranks 3 or 4)	--	Confirmed (Alcohol Ranks 3 or 4)	Confirmed-excessive or Unknown (Alcohol Ranks 2 or 4)	Confirmed-excessive (Alcohol Rank 4)

a. The CDC Guidelines only address FAS.

b. 4-Digit Code: Domains may include, but are not limited to: executive function, memory, cognition, social/adaptive skills, academic achievement, language, motor, attention, or activity level.

c. Canadian: Impairment indicates scores ≥ 2 SDs below the mean, discrepancies of 1.5-2 SDs among subtests, or ≥ 1 SD discrepancy between subdomains.

d. Hoyme: Marked impairment in the performance of complex tasks (complex problem solving, planning, judgment, abstraction, metacognition, and arithmetic tasks); higher-level receptive and expressive language deficits; and disordered behavior (difficulties in personal manner, emotional lability, motor dysfunction, poor academic performance, and deficient social interaction).

e. IOM: Complex pattern of behavior or cognitive abnormalities that are inconsistent with developmental level and cannot be explained by familial background or environment alone: e.g., learning difficulties; deficits in school performance; poor impulse control; problems in social perception; deficits in higher level receptive and expressive language; poor capacity for abstraction or metacognition; specific deficits in mathematical skills; or problems in memory, attention or judgment.

The equivalent 4-Digit Ranks for Growth, Face, CNS and Alcohol are inserted in red font to facilitate comparison across the guidelines.

Why are there four separate guidelines? Their existence reflects the ongoing debate on how best to approach FASD diagnosis. All present with strengths and limitations. Each was developed under different circumstances that influenced their outcome. The 4-Digit Code was investigator initiated in a statewide clinical/research arena using a clinical sample of 1,014 individuals of all races and ages (birth to 51 years of age) [14]. Empirical methods were used both to develop [20,39] and validate the performance of the 4-Digit Code [7-9,14,20,39]. The CDC [36] and Canadian [37] guidelines were federally mandated and commanded a more consensus-driven process. These guidelines were not empirically validated prior to publication. The Hoyme [19] guidelines were also investigator initiated in a clinical/research arena, using a clinical sample of 164 Native American and South African children to augment an existing set of guidelines: the IOM Guidelines.

Table 3. ARND (or its equivalent: Static Encephalopathy/Alcohol Exposed or Neurobehavioral Disorder/Alcohol Exposed) diagnostic criteria. Comparison across the five most current FAS/D diagnostic guidelines.

	4-Digit Code (1997-2004)[38]	CDC[a] (2004)[36]	Canadian (2005)[37]	Hoyme (2005)[19]	IOM (1996)[1]
Growth	Normal to deficient (Growth Ranks 1-4)	--	No growth deficiency (Growth Rank 1)	No growth deficiency (Growth Rank 1)	No growth deficiency (Growth Rank 1)
Face	No more than 1 of the following: • PFL ≤ 3rd percentile • Philtrum Rank 4 or 5 • Lip Rank 4 or 5 (Face Ranks 1-2)	--	No FAS facial phenotype (Face Rank 1)	No FAS facial phenotype (Face Rank 1)	Presumably no components of the pattern of FAS characteristic facial anomalies. (Face Rank 1)
CNS	Criteria for "Static Encephalopathy" At least 1 of the following: • Structural/Neurological: (e.g., OFC ≤ 3rd percentile, abnormal structure, seizure disorder, hard signs) • Severe Dysfunction: (3 or more domains[b] of function with impairment 2 or more SDs below the mean) (CNS Rank 3 and/or 4) Criteria for "Neurobehavioral Disorder"[c] • No Structural/Neurological abnormalities. • Moderate Dysfunction: (1-2 domains[b] of function with impairment ≥ 1.5 SDs below the mean) (CNS Rank 2)	--	At least 3 of the following Structure/Neurological/ Functional domains with significant impairment[c]: • Hard/soft signs, structure, cognition, communication, academic achievement, memory, executive functioning, abstract reasoning, ADD, adaptive behavior, social skills, or communication (CNS Ranks 3-4)	At least 1 of the following: • Structural ○ OFC ≤ 10th percentile ○ Abnormal structure • Dysfunction ○ Complex pattern[d] of behavior / cognitive abnormalities (CNS Ranks 1-4)	At least 1 of the following: • Structural/Neurological: ○ Decreased cranial size at birth ○ Abnormal structure ○ Hard/soft signs • Dysfunction ○ Complex pattern[e] of behavior / cognitive abnormalities (CNS Ranks 2-4)
Additional Criteria	The term ARND is not used. The following terms are used in lieu of ARND: Static Encephalopathy (Severe dysfunction) Neurobehavioral Disorder (Moderate dysfunction)	--	--	--	--
Alcohol	Confirmed (Alcohol Ranks 3 or 4)	--	Confirmed (Alcohol Ranks 3 or 4)	Confirmed-excessive (Alcohol Rank 4)	Confirmed-excessive (Alcohol Rank 4)

a. The CDC Guidelines only address FAS.

b. 4-Digit Code: Domains may include, but are not limited to: executive function, memory, cognition, social/adaptive skills, academic achievement, language, motor, attention, or activity level. MRI research confirms Neurobehavioral Disorder/Alcohol Exposed is a distinct, clinically meaningful subclassification under the umbrella of FASD [9]

c. Canadian: Impairment indicates scores ≥ 2 SDs below the mean, discrepancies of 1.5-2 SDs among subtests, or ≥ 1 SD discrepancy between subdomains.

d. Hoyme: Marked impairment in the performance of complex tasks (complex problem solving, planning, judgment, abstraction, metacognition, and arithmetic tasks); higher-level receptive and expressive language deficits; and disordered behavior (difficulties in personal manner, emotional lability, motor dysfunction, poor academic performance, and deficient social interaction)

e. IOM: Complex pattern of behavior or cognitive abnormalities that are inconsistent with developmental level and cannot be explained by familial background or environment alone: e.g., learning difficulties; deficits in school performance; poor impulse control; problems in social perception; deficits in higher level receptive and expressive language; poor capacity for abstraction or metacognition; specific deficits in mathematical skills; or problems in memory, attention or judgment.

The equivalent 4-Digit Ranks for Growth, Face, CNS and Alcohol are inserted in red font to facilitate comparison across the guidelines.

Each guideline is introduced below. Since the circumstances that surrounded the development of each guideline influenced its outcome, it seemed most appropriate to let each guideline introduce itself (the published abstract or executive summary of each is presented below, with permission).

Table 4. ARBD diagnostic criteria. Comparison across the five most current FAS/D diagnostic guidelines.

	4-Digit Code[a] (1997-2004) [38]	CDC[b] (2004) [36]	Canadian[a] (2005) [37]	Hoyme (2005) [19]	IOM (1996) [1]
Growth	--	--	--	Not specified (Growth Rank ?)	Not specified (Growth Rank ?)
Face	--	--	--	2 or more of the following: • PFL ≤ 10th percentile • Philtrum Rank 4 or 5 • Lip Rank 4 or 5 (Face Ranks 2-4)	Not specified (Face Rank ?)
CNS	--	--	--	Not specified (CNS Rank ?)	Not specified (CNS Rank ?)
Congenital Defects	--	--	--	1 or more of the following: • Cardiac: Atrial septal defects, Ventricular septal defects, Aberrant great vessels, Tetralogy of Fallot. • Skeletal: Hypoplastic nails, Shortened fifth digits, Radioulnar synostosis, Flexion contractures, Camptodactyly, Clinodactyly, Pectus excavatum and carinatum, Klippel-Feil syndrome, Hemivertebrae, Scoliosis. • Renal: Aplastic/dysplastic/hypoplastic kidneys, Horseshoe kidneys, Ureteral duplications, Hydronephrosis. • Ocular: Strabismus, Retinal vascular anomalies, Refractive problems secondary to small globes. • Auditory: Conductive hearing loss, Neurosensory hearing loss. • Other: Virtually every malformation has been described in some patient with FAS. The etiologic specificity of most of these anomalies to alcohol teratogenesis remains uncertain.	Congenital structural defects in 1 of the following categories, including malformations and dysplasias (if the patient displays minor anomalies only, 2 must be present): • Cardiac: Atrial septal defects, Ventricular septal defects, Aberrant great vessels, conotruncal heart defects. • Skeletal: Radioulnar synostosis, Vertebral segmentation defects, Large joint contractures, Scoliosis. • Renal: Aplastic/dysplastic/hypoplastic kidneys, "Horseshoe" kidney/ureteral duplications. • Eyes: Strabismus, Ptosis, Retinal vascular anomalies, Optic nerve hypoplasia. • Ears: Conductive hearing loss, Neurosensory hearing loss. • Minor Anomalies: Hypoplastic nails, Short fifth digits, Clinodactyly of fifth fingers, Pectus carinatum / excavatum, Camptodactyly, "Hockey stick" palmar creases, Refractive errors, "Railroad track" ears.
Alcohol	--	--	--	Confirmed-excessive (Alcohol Rank 4)	Confirmed-excessive (Alcohol Rank 4)

a. The 4-Digit Code and Canadian Guidelines do not recognize ARBD as a FASD diagnostic classification.

b. The CDC Guidelines only address FAS.

The equivalent 4-Digit Ranks for Growth, Face, CNS and Alcohol are inserted in red font to facilitate comparison across the guidelines.

To facilitate comparisons across the five guidelines, the FAS criteria used by the 4-Digit Code [38], CDC [36], Canadian [37], Hoyme [19], and IOM [1] guidelines are presented in Table 1. The same format is used to present the criteria for PFAS, ARND, and ARBD (Tables 2-4 respectively).

It is important to note that for the purposes of this chapter, the 4-Digit Code has been translated, as best as possible, into a text, rather than numeric, format across Tables 1-4. This was done to facilitate comparison to the other guidelines that publish their diagnostic criteria in text format. Diagnostic teams should not use the textual translations of the 4-Digit Code presented in Tables 1-4 to derive a 4-Digit Code. Diagnostic teams should use the numeric format presented in the 2004 Diagnostic Guide [38].

FASD 4-Digit Code (1997, 1999, Nov 2004) [34,35,38]

Rationale for the FASD 4-Digit Code

One year after the release of the 1996 IOM guidelines [1], the FASD 4-Digit Diagnostic Code was created [14,34,35,38] to address the following limitations in the extant gestalt approach to FASD diagnosis.

1. *There have been no standardized operational definitions for FAS or for any of the other diagnoses that fall under the umbrella of FASD. Rather, there have been diagnostic guidelines that physicians have been encouraged to follow, but the guidelines have not been sufficiently specific to assure diagnostic accuracy or precision.*

For example, according to the diagnostic guidelines published by Sokol and Clarren [5], which were a minor modification of the 1980 definition of FAS by the Fetal Alcohol Study Group of the Research Society for Alcoholism [3], which, in turn, were derived from the work of Clarren and Smith [4]: "The diagnosis of FAS can only be made when the patient has signs of abnormality in each of the three categories: 1) Prenatal and/or postnatal growth retardation [weight and/or length below the 10th percentile when corrected for gestational age], 2) central nervous system involvement (including neurological abnormality, developmental delay, behavioral dysfunction or deficit, intellectual impairment, and/or structural abnormalities, such as microcephaly [head circumference below the 3rd percentile or brain malformations found on imaging studies or autopsy] and 3) a characteristic face, currently qualitatively described as including short palpebral fissures, an elongated midface, a long and flattened philtrum, thin upper lip, and flattened maxilla."

The 1996 guidelines for the diagnosis of FAS proposed by the IOM [1] took a similar approach. The diagnosis of FAS can be made when the patient presents with: "1) Evidence of growth retardation, as in at least one of the following: a) low birth weight for gestational age; b) decelerating weight over time not due to nutrition; or c) disproportional low weight to height; 2) Evidence of a characteristic pattern of facial anomalies that includes features such as short palpebral fissures and abnormalities in the premaxillary zone (e.g., flat upper lip, flattened philtrum, and flat midface); and 3) Evidence of CNS neurodevelopmental abnormalities, as in at least one of the following: a) decreased cranial size at birth; b) structural brain abnormalities (e.g., microcephaly, partial or complete agenesis of the corpus callosum, cerebellar hypoplasia);c) neurological hard or soft signs (as age appropriate), such as impaired fine motor skills, neurosensory hearing loss, poor tandem gait, poor eye-hand coordination."

Although these descriptions do provide guidance, they are not sufficiently specific to assure diagnostic accuracy and precision. They reflect a gestalt approach to diagnosis. The guidelines for CNS abnormalities do not address how many areas of deficit must be present, how severe the deficits must be, or what level of documentation must exist to substantiate the presence of the deficit. The guidelines for the facial phenotype are equally nonspecific. How many facial features must be present, how severe must the features be, and what scale of measurement should be used to judge the severity? One need only read the clinical literature or review medical records, birth certificates, birth defect registries or ICD-9 codes to see how variably these criteria are interpreted, applied and reported [1,40-43].

2. *There has been a lack of objective, quantitative scales to measure and report the magnitude of expression of key diagnostic features*

For example, although a thin upper lip and smooth philtrum are key diagnostic features [1,2,4,39,44], quantitative measurement scales were never used to measure thinness or smoothness, and guidelines had never been established for how thin or smooth the features must be. Objective quantitative scales not only improve accuracy and precision, but also establish a common numeric language for communicating outcomes in medical records and in the medical literature.

3. *The term fetal alcohol effects (FAE) was broadly used and poorly defined.*

The term 'suspected fetal alcohol effects' was first introduced into the medical literature in 1978 and was defined as 'less complete partial expressions' of FAS in individuals with prenatal alcohol exposure [4]. Based on this definition, an individual whose mother drank a few glasses of wine intermittently throughout pregnancy and presented with attention deficit hyperactivity disorder would meet the criteria for FAE. So would an individual whose mother drank a fifth of vodka daily throughout pregnancy and presented with microcephaly, severe mental retardation, growth deficiency and no facial anomalies. The broad use of this term and the reluctance to abandon it points to the clear need to develop diagnostic terms for individuals with prenatal alcohol exposure who present with physical anomalies and/or cognitive/behavioral disabilities, but do not meet the criteria for FAS. New diagnostic terms that more finely differentiate the variable exposures and outcomes of individual patients, without implying alcohol as the sole causal agent, were needed.

4. *Clinical terms like FAE [4,5], alcohol-related birth defects (ARBD) [1] and alcohol-related neurodevelopmental disorder (ARND) [1] imply a causal link between alcohol exposure and outcome*

in a given individual that cannot be medically confirmed. Leading dysmorphologists in the field of FAS diagnosis have formally requested that the term FAE no longer be used for this reason[13].

With the likely exception of the full facial phenotype, no other physical anomalies or cognitive/behavioral disabilities observed in an individual with prenatal alcohol exposure are necessarily specific to (caused only by) their prenatal alcohol exposure [1]. Features such as microcephaly, neurological abnormalities, attention deficit, mental retardation, and growth deficiency frequently occur in individuals with prenatal alcohol exposure, and frequently occur in individuals with no prenatal alcohol exposure. The diagnostic terms ARBD and ARND introduce the same limitation as does FAE, namely, implying alcohol exposure caused the birth defect or neurobehavioral disorder in an individual patient.

5. *Too often diagnoses depicting FASD are reported in the medical records and scientific literature with no documentation of the method used to derive the diagnosis and little or no documentation of the data used to render/support the diagnosis.*

Failure to report this information can limit the patient's ability to qualify for and receive appropriate intervention services from subsequent health care, social service, and educational providers. For example, simply reporting that an individual has FAS does little to convey the individual's strengths and disabilities. Some individuals with FAS have low IQs, some have IQs in the normal range, some have attention deficits, some do not, some have problems with memory, while others have language deficits. From a public health perspective, failure to report these data also prevents surveillance efforts from accurately tracking the prevalence of FASD diagnoses in the population. The supportive data are needed to validate the diagnoses. Accurate surveillance is vital for setting public health policy and assessing the effectiveness of primary prevention efforts. The 4-Digit Code requires that data be collected not just to support the diagnosis, but to derive the diagnosis. The 4-Digit Code provides a comprehensive FASD Diagnostic Form for recording all supportive data and provides a numeric classification scheme that is readily incorporated into clinical, research, and surveillance databases.

6. *FAS is a medical diagnosis and thus has historically been diagnosed by a medical doctor (e.g., dysmorphologist, geneticist). There is now clear consensus that an interdisciplinary team approach is superior [32,35-37].*

Each of the above limitations was largely overcome with the development of the FASD 4-Digit Diagnostic Code in 1997[35]. Briefly, the 4 digits of the FASD 4-Digit Code reflect the magnitude of expression of the 4 key diagnostic features of FASD, in the following order: (1) growth deficiency, (2) FAS facial phenotype, (3) CNS structural/functional abnormalities, and (4) prenatal alcohol exposure (Figs. 2 and 3). The magnitude of expression of each feature is ranked independently on a 4-point Likert scale, with 1 reflecting complete absence of the FASD feature and 4 reflecting a strong "classic" presence of the FASD feature. Each Likert rank is specifically case defined. For example if a patient received the following Ranks: Growth = 3, Face = 4, CNS = 4, Alcohol = 4; the resulting 4-Digit Code would be 3444. Code 3444 is one of twelve 4-Digit Codes that meet the criteria for FAS/Alcohol Exposed (Fig. 2). An interactive, electronic FASD 4-Digit Code Short Form [45] is provided (Fig. 4) to demonstrate the simple, numeric approach used by the 4-Digit Code to define and derive a diagnosis. There are 256 possible 4-digit diagnostic codes, ranging from 1111 (reflecting complete absence of growth deficiency, FAS facial features, CNS abnormalities, and alcohol exposure) to 4444 (reflecting the most severe presentation of FAS: severe growth deficiency, the full FAS facial phenotype, significant CNS abnormalities, and high exposure to alcohol). Each 4-Digit diagnostic code falls into 1 of 22 unique clinical diagnostic categories (labeled A through V). Seven of the 22 diagnostic categories (4-Digit Categories A–C and E–H) fall broadly under the umbrella of FASD (A. FAS/Alcohol Exposed B. FAS/Alcohol Exposure Unknown, C. Partial FAS/Alcohol Exposed, E-F. Static Encephalopathy/Alcohol Exposed, and G-H. Neurobehavioral Disorder/Alcohol Exposed) (Fig. 2).

The FASD 4-Digit Diagnostic Code was developed from the clinical records of 1,014 patients of all races and ages evaluated by the FAS DPN interdisciplinary team at the University of Washington. The purpose was not to redefine, but rather, more specifically case-define the key diagnostic components of FAS as presented across several previously published FAS diagnostic guidelines [1,3-5]. The performance of the 4-Digit Code was validated prior to

FASD 4-Digit Diagnostic Code

		3	4	4		4
RANK	4	Severe	Severe	Definite		High risk
	3	Moderate	Moderate	Probable		Some Risk
	2	Mild	Mild	Possible		Unknown
	1	None	None	Unlikely		No Risk
		Growth Deficiency	**FAS Facial Features**	**CNS Damage**		**Prenatal Alcohol**

Digit Diagnostic Codes within each FASD Diagnostic Category

A. FAS / Alcohol Exposed

2433	3433	4433
2434	3434	4434
2443	3443	4443
2444	3444	4444

B. FAS / Alcohol Exposure Unknown

2432	3432	4432
2442	3442	4442

C. Partial FAS /Alcohol Exposed

1333	1433	2333	3333	4333
1334	1434	2334	3334	4334
1343	1443	2343	3343	4343
1344	1444	2344	3344	4344

E. Sentinel Physical Finding(s) / Static Encephalopathy / Alcohol Exposed

3133	3233	4133	4233
3134	3234	4134	4234
3143	3243	4143	4243
3144	3244	4144	4244

F. Static Encephalopathy / Alcohol Exposed

1133	1233	2133	2233
1134	1234	2134	2234
1143	1243	2143	2243
1144	1244	2144	2244

G. Sentinel Physical Finding(s) / Neurobehavioral Disorder / Alcohol Exposed

1323	2323	3123	3323	4123	4323
1324	2324	3124	3324	4124	4324
1423	2423	3223	3423	4223	4423
1424	2424	3224	3424	4224	4424

H. Neurobehavioral Disorder / Alcohol Exposed

1123	1223	2123	2223
1124	1224	2124	2224

I. Sentinel Physical Finding(s) / Alcohol Exposed

1313	2313	3113	3313	4113	4313
1314	2314	3114	3314	4114	4314
1413	2413	3213	3413	4213	4413
1414	2414	3214	3414	4214	4414

J. No Physical Findings or CNS Abnormalities Detected / Alcohol Exposed

1113	1213	2113	2213
1114	1214	2114	2214

Figure 2: The 4-Digit Code is derived by ranking the severity of growth deficiency, FAS facial features, CNS abnormality, and alcohol exposure on 4-point Likert scales. Each rank is specifically case-defined [38]. The 4-Digit Code 3444 is one of twelve 4-Digit Codes that meet the diagnostic criteria for FAS / Alcohol Exposed.

its release [14]. Its performance was compared to the standard gestalt method of diagnosis on the first 454 patients who had received a gestalt diagnosis of FAS, PFAS or possible fetal alcohol effect (PFAE) prior to the development of the 4-Digit Code.

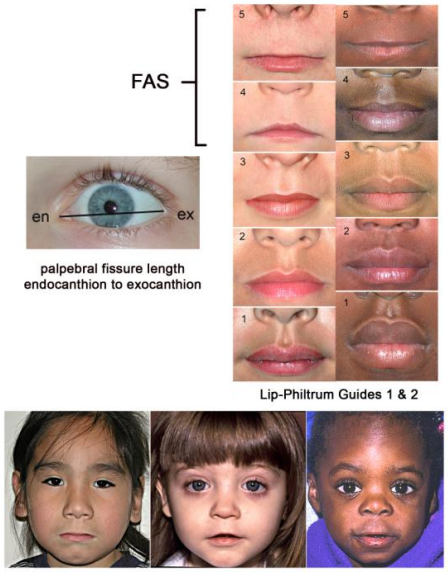
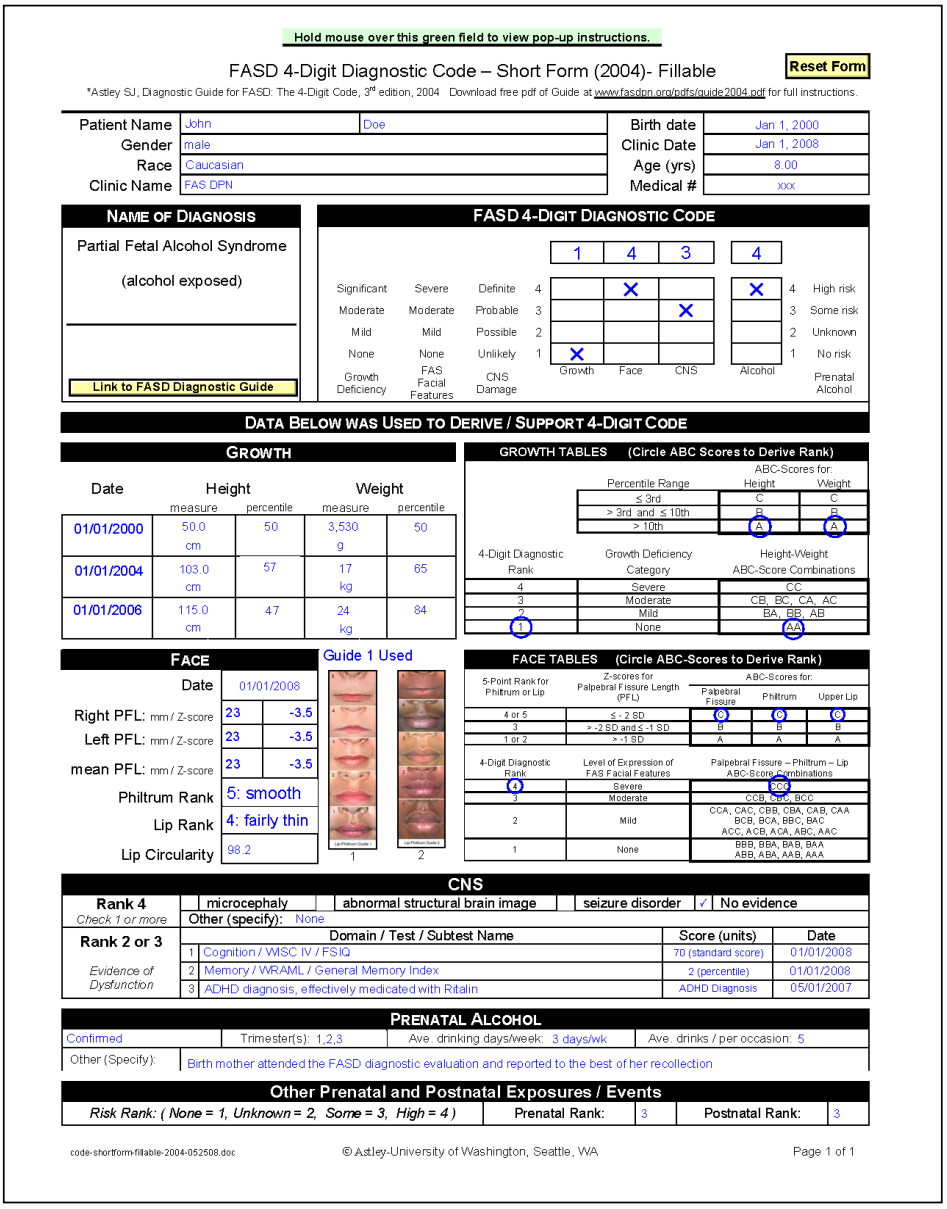


Figure 3: FASD 4-Digit Code FAS facial phenotype. The Rank 4 FAS facial phenotype determined with the 4-Digit Diagnostic Code requires the presence of all 3 of the following anomalies: (1) palpebral fissure length 2 or more standard deviations below the norm; (2) smooth philtrum (Rank 4 or 5 on the Lip-Philtrum Guide), and (3) thin upper lip (Rank 4 or 5 on the Lip-Philtrum Guide). Examples of the Rank 4 FAS facial phenotype for Native American, Caucasian, and African American children are shown. Copyright: Susan Astley, University of Washington, Seattle, WA.

The FASD 4-Digit Diagnostic Code:

1. Greatly increased diagnostic precision and accuracy through the development of objective, quantitative measurement scales (e.g., Lip-Philtrum Guides), facial analysis software, and specific case definitions.
2. Diagnosed the full spectrum of outcomes across the lifespan.
3. Offered an intuitively logical numeric approach to reporting outcomes and exposure that reflects the true diversity and continuum of disability observed in individuals with prenatal alcohol exposure.
4. Established a method for case-defining the highly variable, nonspecific CNS dysfunction that typifies FASD, by quantifying the breadth and magnitude of dysfunction (number of domains of function 2 or more SDs below the mean) without unduly constraining which domains must be impaired.
5. Established diagnostic subclassifications that captured the full spectrum of FASD without inferring alcohol is the sole causal agent.
6. Documents all other prenatal and postnatal adverse exposures and events that can also impact outcome.
7. Provides a quantitative measurement and reporting system (the 4-Digit Code) that can be used independent of the diagnostic nomenclature.
8. Has received extensive assessment/validation of its performance.
9. Was designed for use by an interdisciplinary FASD diagnostic team.
10. Is readily taught to a wide array of health care and social service providers (e.g., FASD 4-Digit Code Online Course[46]), thus greatly expanding the availability of diagnostic services.



Hold mouse over this green field to view pop-up instructions.

FASD 4-Digit Diagnostic Code – Short Form (2004)- Fillable

Reset Form

*Astley SJ, Diagnostic Guide for FASD: The 4-Digit Code, 3rd edition, 2004 Download free pdf of Guide at www.fasdpn.org/pdfs/guide2004.pdf for full instructions.

Patient Name	John	Doe	Birth date	Jan 1, 2000
Gender	male		Clinic Date	Jan 1, 2008
Race	Caucasian		Age (yrs)	8.00
Clinic Name	FAS DPN		Medical #	xxx

NAME OF DIAGNOSIS

Partial Fetal Alcohol Syndrome

(alcohol exposed)

Link to FASD Diagnostic Guide

FASD 4-DIGIT DIAGNOSTIC CODE

				Growth	Face	CNS	Alcohol		
				1	4	3	4		
Significant	Severe	Definite	4		X		X	4	High risk
Moderate	Moderate	Probable	3			X		3	Some risk
Mild	Mild	Possible	2					2	Unknown
None	None	Unlikely	1	X				1	No risk
Growth Deficiency	FAS Facial Features	CNS Damage							Prenatal Alcohol

DATA BELOW WAS USED TO DERIVE / SUPPORT 4-DIGIT CODE

GROWTH

Date	Height measure	Height percentile	Weight measure	Weight percentile
01/01/2000	50.0 cm	50	3,530 g	50
01/01/2004	103.0 cm	57	17 kg	65
01/01/2006	115.0 cm	47	24 kg	84

GROWTH TABLES (Circle ABC Scores to Derive Rank)

Percentile Range	ABC-Scores for: Height	Weight
≤ 3rd	C	C
> 3rd and ≤ 10th	B	B
> 10th	(A)	(A)

4-Digit Diagnostic Rank	Growth Deficiency Category	Height-Weight ABC-Score Combinations
4	Severe	CC
3	Moderate	CB, BC, CA, AC
2	Mild	BA, BB, AB
(1)	None	(AA)

FACE

Guide 1 Used

Date	01/01/2008	
Right PFL: mm / Z-score	23	-3.5
Left PFL: mm / Z-score	23	-3.5
mean PFL: mm / Z-score	23	-3.5
Philtrum Rank	5: smooth	
Lip Rank	4: fairly thin	
Lip Circularity	98.2	

1 2

FACE TABLES (Circle ABC-Scores to Derive Rank)

5-Point Rank for Philtrum or Lip	Z-scores for Palpebral Fissure Length (PFL)	ABC-Scores for: Palpebral Fissure	Philtrum	Upper Lip
4 or 5	≤ -2 SD	(C)	(C)	(C)
3	> -2 SD and ≤ -1 SD	B	B	B
1 or 2	> -1 SD	A	A	A

4-Digit Diagnostic Rank	Level of Expression of FAS Facial Features	Palpebral Fissure – Philtrum – Lip ABC-Score Combinations
(4)	Severe	(CCC)
3	Moderate	CCB, CBC, BCC
2	Mild	CCA, CAC, CBB, CBA, CAB, CAA BCB, BCA, BBC, BAC ACC, ACB, ACA, ABC, AAC
1	None	BBB, BBA, BAB, BAA ABB, ABA, AAB, AAA

CNS

Rank 4 Check 1 or more	microcephaly	abnormal structural brain image	seizure disorder	✓ No evidence
	Other (specify): None			

Rank 2 or 3 Evidence of Dysfunction	Domain / Test / Subtest Name	Score (units)	Date
1	Cognition / WISC IV / FSIQ	70 (standard score)	01/01/2008
2	Memory / WRAML / General Memory Index	2 (percentile)	01/01/2008
3	ADHD diagnosis, effectively medicated with Ritalin	ADHD Diagnosis	05/01/2007

PRENATAL ALCOHOL

Confirmed	Trimester(s): 1,2,3	Ave. drinking days/week: 3 days/wk	Ave. drinks / per occasion: 5
Other (Specify):	Birth mother attended the FASD diagnostic evaluation and reported to the best of her recollection		

Other Prenatal and Postnatal Exposures / Events

Risk Rank: (None = 1, Unknown = 2, Some = 3, High = 4)	Prenatal Rank:	3	Postnatal Rank:	3

code-shortform-fillable-2004-052508.doc © Astley-University of Washington, Seattle, WA Page 1 of 1

Figure 4: FASD 4-Digit Diagnostic Code Short Form. In lieu of the more comprehensive 7-page FASD Diagnostic Form, some clinics may prefer to use the **1-page FASD 4-Digit Short Form**. The Short Form allows a clinician to record the minimum amount of data required to derive/support the 4-Digit Code. Diagnostic teams who do not have the time/capacity to complete the more comprehensive form will find this electronic, interactive, Short Form helpful.

The 4-Digit Code has served as the cornerstone of a fully integrated and highly successful screening, diagnostic, intervention, prevention, and surveillance program in Washington State for the past 17 years [7,8,18,1,47-49]. A comprehensive profile of all patients receiving an interdisciplinary FASD diagnostic evaluation using the 4-Digit Code at the Washington State FAS Diagnostic and Prevention network (WA FAS DPN) clinic in the first 12 years of operation is presented in the Astley paper [50]. Hundreds of FASD diagnostic teams have been trained worldwide to use this interdisciplinary FASD diagnostic system [46].

CDC FAS Guidelines, July 2004 [36]

In 2004 the CDC published the following Executive Summary to introduce the CDC FAS guidelines (p. vii-ix, with permission) [36]:

"As part of the fiscal year 2002 appropriations funding legislation, the U.S. Congress mandated that the Centers for Disease Control and Prevention (CDC), acting through the National Center on Birth Defects and Developmental Disabilities (NCBDDD) Fetal Alcohol Syndrome (FAS) Prevention Team and in coordination with the National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effect (NTFFAS/FAE), other federally funded FAS programs, and appropriate nongovernmental organizations, would:

Develop guidelines for the diagnosis of FAS and other negative birth outcomes resulting from prenatal exposure to alcohol,

Incorporate these guidelines into curricula for medical and allied health students and practitioners, and seek to have them fully recognized by professional organizations and accrediting boards, and

Disseminate curricula to and provide training for medical and allied health students and practitioners regarding these guidelines.

Through the coordinated efforts of CDC, the NTFFAS/FAE, and a scientific working group (SWG) of experts in FAS research, diagnosis, and treatment, the diagnostic criteria were developed over a 2-year period.

A primary goal of these guidelines is to provide standard diagnostic criteria for FAS so that consistency in the diagnosis can be established for clinicians, scientists, and service providers. The guidelines are based on state-of-the-art scientific research, clinical expertise, and family input regarding the physical and neuropsychological features of FAS. The SWG sought to harmonize these guidelines with other diagnostic systems currently in use in this country and others (e.g., Canada). The SWG strove to provide a balance between conservative and overly inclusive diagnostic systems. Differential diagnosis from other genetic, teratological, and behavioral disorders was emphasized.

These guidelines are not intended to be an endpoint in the discussion of diagnosing FAS. There is a great need to acquire science-based information that will facilitate diagnostic criteria for additional related disorders, such as Alcohol Related Neurodevelopmental Disorder (ARND). These guidelines conclude with a call for further research and continuous refinement of the diagnostic criteria for FAS and related conditions so that affected individuals and their families can receive important services that enable them to achieve healthy lives and reach their full potential."

Hoyme FASD Guidelines, January 2005 [19]

In 2005, Hoyme et al [19] published the following abstract (p. 39, with permission) to introduce their FASD guidelines:

"The adverse effects of alcohol on the developing human represent a spectrum of structural anomalies and behavioral and neurocognitive disabilities, most accurately termed fetal alcohol spectrum disorders (FASD). The first descriptions in the modern medical literature of a distinctly recognizable pattern of malformations associated with maternal alcohol abuse were reported in 1968 and 1973. Since that time, substantial progress has been made in developing specific criteria for defining and diagnosing this condition. Two sets of diagnostic criteria are now used most widely for evaluation of children with potential diagnoses in the FASD continuum, ie, the 1996 IOM [1] criteria and the Washington criteria. Although both approaches have improved the clinical delineation of FASD, both suffer from significant drawbacks in their practical application in pediatric practice. Objective. The purpose of this report is to present specific clarifications of the 1996 IOM criteria [1] for the diagnosis of FASD, to facilitate their practical application in clinical pediatric practice. A large cohort of children who were prenatally exposed to alcohol were identified, through active case-ascertainment methods, in 6 Native American communities in the United States and 1 community in the Western Cape Province of South Africa. The children and their families underwent standardized multidisciplinary evaluations, including a dysmorphology examination, developmental and neuropsychologic testing,

and a structured maternal interview, which gathered data about prenatal drinking practices and other demographic and family information. Data for these subjects were analyzed, and revisions and clarifications of the existing IOM FASD diagnostic categories were formulated on the basis of the results. The revised IOM method defined accurately and completely the spectrum of disabilities among the children in our study. On the basis of this experience, we propose specific diagnostic criteria for fetal alcohol syndrome and partial fetal alcohol syndrome. We also define alcohol-related birth defects and alcohol-related neurodevelopmental disorder from a practical standpoint. The 1996 IOM criteria [1] remain the most appropriate diagnostic approach for children prenatally exposed to alcohol. The proposed revisions presented here make these criteria applicable in clinical pediatric practice. "

Canadian FASD Guidelines, March 2005 [37]

In 2005 Chudley et al [37] published the following abstract (p. s1) to introduce the Canadian FASD guidelines:

"A subcommittee of the Public Health Agency of Canada's National Advisory Committee on Fetal Alcohol Spectrum Disorder reviewed, analyzed and integrated current approaches to diagnosis to reach agreement on a standard in Canada. The purpose of this paper is to review and clarify the use of current diagnostic systems and make recommendations on their application for diagnosis of FASD-related disabilities in people of all ages. The guidelines are based on widespread consultation of expert practitioners and partners in the field. The guidelines have been organized into 7 categories: screening and referral; the physical examination and differential diagnosis; the neurobehavioural assessment; and treatment and follow-up; maternal alcohol history in pregnancy; diagnostic criteria for fetal alcohol syndrome (FAS), partial FAS and alcohol-related neurodevelopmental disorder; and harmonization of Institute of Medicine and 4-Digit Diagnostic Code approaches. The diagnosis requires a comprehensive history and physical and neurobehavioural assessments; a multidisciplinary approach is necessary. These are the first Canadian guidelines for the diagnosis of FAS and its related disabilities, developed by broad-based consultation among experts in diagnosis."

Comparison of Current Guidelines

An interdisciplinary approach to FASD diagnosis using more rigorously case-defined guidelines, as originally proposed by the WA FAS DPN [14,32,35] was adopted in principal in all subsequent guidelines. Key contrasts do exist, however (Tables 1-4). Of the guidelines currently in use, the FASD 4-Digit Code[38] and Canadian FASD guidelines [37] are most similar. Both systems cover the full spectrum of diagnostic outcomes, use FAS facial criteria with confirmed high specificity to prenatal alcohol exposure, and adhere to strict criteria that use the standard medical/statistical definition of "abnormal" (2 or more SDs below the mean or its equivalent $\leq 2.5^{th}$ percentile) [51]. In contrast to the 4-Digit Code and Canadian guidelines, the CDC guidelines [36] address only FAS; have more relaxed facial criteria (with unknown specificity); and have more relaxed CNS criteria (using diagnostic cutoff values for "abnormal" of 1 SD below the mean or $\leq 10^{th}$ percentile). The Hoyme guidelines [19], while addressing the full spectrum of outcomes, diverge considerably from the 4-Digit Code, CDC, and Canadian guidelines, but are closely aligned with the IOM guidelines [1] from which they were derived. For the diagnosis of FAS, the Hoyme guidelines further relax the facial criteria requiring only 2 of the 3 diagnostic features be present while allowing the palpebral fissure length (PFL) to move further into the normal range ($\leq 10^{th}$ percentile). This results in facial criteria that are no longer specific to prenatal alcohol exposure [16]. The Hoyme guidelines for FAS also restrict the CNS criteria to structural abnormalities only; and relax the criterion for small head circumference from the medical definition of microcephaly ($\leq 2.5^{th}$ percentile) [52] to $\leq 10^{th}$ percentile. All 4 sets of guidelines require prenatal alcohol exposure to be documented, but allow a diagnosis of FAS to be rendered if prenatal alcohol exposure is unknown. The Hoyme guidelines, like the IOM guidelines, go further by requiring that the confirmed exposure be "excessive" (e.g., characterized by substantial regular intake or heavy episodic drinking). Features unique to each guideline are: 1) The 4-Digit Code does not use the term ARND and is the only guideline that measures all four features of FAS (growth, face, CNS, and alcohol exposure) on continuous scales; 2) The Canadian guidelines require severe CNS dysfunction be present for a diagnosis of FAS; and 3) The Hoyme guidelines use only physical features to define FAS.

Diagnostic Nomenclature

A number of terms have been established over the years to label the diagnostic subclassifications under the umbrella of FASD. These include FAS, PFAS ARND, Static Encephalopathy/Alcohol Exposed (SE/AE),

Neurodevelopmental Disorder/Alcohol Exposed (ND/AE), Alcohol Related Birth Defects (ARBD), and Fetal Alcohol Effects (FAE). Table 5 presents each term, the clinical features that delineate each term, and which guidelines use the terms.

Table 5: FASD diagnostic terms, the clinical features that define each term, and which FAS/D guidelines use each term.

FASD Diagnostic Terms	Clinical Features Present					Guidelines That Use the Term				
	Growth Deficiency	FAS Facial Phenotype	CNS Abnormality	Prenatal Alcohol Exposure	Other Congenital Defects	4-Digit[38]	CDC[a][36]	Canadian[37]	Hoyme[19]	IOM[1]
FAS	Yes	Yes	Yes	Yes or Unknown		■	■	■	■	■
PFAS	Yes or No	Yes (Full or Partial)	Yes or No[b]	Yes or Unknown[c]		■	-	■	■	■
ARND			Yes	Yes			-	■	■	■
SE/AE			Yes, Severe	Yes		■	-			
ND/AE			Yes, Moderate	Yes		■	-			
ARBD		Yes and No[d]		Yes	Yes		-		■	■
FAE[e]			Yes	Yes			-			

a. (-) CDC guidelines currently address only FAS.
b. The Hoyme and IOM guidelines allow PFAS to be diagnosed in the absence of CNS abnormality.
c. Only the Hoyme guidelines allow an unknown alcohol exposure for PFAS.
d. The Hoyme guidelines require the FAS facial phenotype be present for ARBD. The IOM guidelines do not.
e. Used in the Sokol & Clarren FASD guidelines [5]

Issues to Consider

The following issues are important to consider as one assesses the strengths/limitations of the current FAS/D diagnostic guidelines.

Why are the criteria used to define the FAS facial phenotype so important to the medical validity of a FAS diagnosis? When one makes a diagnosis of FAS, one is stating implicitly that the individual has a syndrome caused by prenatal alcohol exposure[16]. One is also stating implicitly that the biological mother drank alcohol during pregnancy and, as a result, harmed her child. These are bold conclusions to draw and are not without medical and ethical consequences. How confident can one be when one infers a causal link between an individual's prenatal alcohol exposure and his or her syndromic features, especially when 2 of the 3 diagnostic features of this syndrome (growth deficiency and CNS damage/dysfunction) are not specific to (caused only by) prenatal alcohol exposure. The validity of the diagnosis rests solely on the specificity of the facial phenotype to the exposure (alcohol) and to the outcome (FAS). If a cluster of facial features is truly unique to prenatal alcohol exposure (e.g., alcohol is the only agent that can cause this facial phenotype) and is unique to the diagnosis of FAS (e.g., this exact phenotype is not present in any other medical condition), then one would expect to observe the following: (1) the face would be highly sensitive to FAS (e.g., individuals with FAS would have the FAS facial phenotype), (2) the face would be highly specific to FAS (e.g., individuals without FAS would not have the FAS facial phenotype), and (3) the face would be highly specific to prenatal alcohol exposure (e.g., individuals without prenatal alcohol exposure would not have the FAS facial phenotype). The rank 4 FAS facial phenotype, as defined by the 4-Digit Code, demonstrates all three of these qualities [7,9,16,20,39].

A highly specific FAS facial phenotype validates the FAS diagnosis, because the presence of the face confirms that an individual was affected, at least in part, by their prenatal alcohol exposure. The face also confirms the individual was exposed to alcohol. The latter is used to render a diagnosis of FAS in the absence of confirmed prenatal alcohol exposure. If the face is truly specific to alcohol, then individuals cannot have the face if they were not exposed to alcohol. This is why all diagnostic guidelines allow FAS to be diagnosed, even when prenatal alcohol exposure is

unknown. When the face is confirmed to be highly specific to alcohol exposure, it can serve as a valid proxy measure for exposure. This is also why diagnostic guidelines cannot and do not allow ARND (or its equivalent) to be diagnosed when alcohol exposure is unknown. Since the FAS facial phenotype is not present in ARND, it cannot serve as a proxy measure for alcohol exposure. In the absence of a highly specific facial phenotype, the validity of the diagnostic process breaks down precipitously; an individual's outcome cannot be linked to their prenatal alcohol exposure, FAS becomes indistinguishable from ARND, and valid diagnoses cannot be made when alcohol exposure is unknown.

Considering the quintessential role the FAS facial phenotype plays in FAS diagnosis, its specificity cannot be assumed, it must be confirmed through properly designed empirical studies. The FAS facial criteria (Rank 4) used by the 4-Digit Code and Canadian Guidelines have confirmed, high sensitivity and specificity (> 95%) [39]. The CDC and Hoyme guidelines have not reported the sensitivity and specificity of their relaxed facial criteria. When the Hoyme criteria were applied to a sample of normal to high functioning children with confirmed absence of prenatal alcohol exposure, 4 of the 16 met the Hoyme criteria for the full FAS facial phenotype [16]. This demonstrates the facial criteria have been relaxed too far.

Should an 'excessive' alcohol exposure be required for diagnoses under the umbrella of FASD? There remains no clear scientific consensus on what quantity, frequency, and duration of exposure is toxic to the fetus. There are a multitude of reasons for this. 1.) As our tools for measuring outcome become more sensitive, our ability to identify adverse outcomes at lower exposures increases [53]. 2.) Risk from alcohol exposure varies between fetuses, even between fraternal twins with ostensibly identical exposure [54, 55]. It is not uncommon for one fraternal twin to have full FAS, while the other appears unaffected. Identical twins are typically identically affected. 3.) From a public health perspective, requiring excessive exposure implies lower levels of exposure are 'safe'. Safe for whom? 4.) From a research perspective, artificially linking outcome to a threshold level of high exposure prevents assessing the true relationship between exposure and outcome. 5.) Finally, from a clinical perspective, if an "excessive" exposure is required, it would be difficult to rationalize why an individual with all the features of FAS would receive a diagnosis of FAS if their exposure was unknown, but would fail to receive a diagnosis of FAS if their exposure was confirmed, but reportedly not excessive. This implies that practitioners have the ability to confirm the accuracy of exposure histories. They do not. "Excessive" alcohol exposures should not be required for FASD diagnoses.

FAE and ARND: The field continues to struggle with what to label the condition characterized by prenatal alcohol exposure and CNS abnormalities when the FAS facial phenotype is absent. The problem with the diagnostic terms used to date (Fetal Alcohol Effects (FAE) and Alcohol-Related Neurodevelopmental Disorder (ARND) is they imply that the patient's outcomes are *alcohol effects* or *alcohol-related* outcomes. They imply alcohol caused the patient's outcomes. But this presumption in an *individual* patient is medically invalid because CNS abnormalities are not specific to (caused only by) prenatal alcohol exposure. There are many other known or unknown risk factors that may be partly or even fully responsible for the patient's outcome. In the absence of the FAS facial phenotype, current medical technology has no ability to confirm or rule-out the etiologic role of alcohol in an *individual* patient.

The term FAE (or more accurately, possible FAE) was first introduced by Clarren and Smith in 1978 [4]. In 1995, Aase, Jones, and Clarren argued effectively that clinical use of the term FAE, with its implications of causation, should be abandoned [13]. In 1996, the IOM [1] acknowledged the concerns expressed by Aase and colleagues [13] and introduced ARND (and ARBD) to replace FAE. But ARND (and ARBD) presented with all the same limitations as FAE. In 1997, the 4-Digit Code introduced Static Encephalopathy/Alcohol Exposed (SE/AE)) and Neurobehavioral Disorder/Alcohol Exposed (NDAE) to replace ARND [35]. These new clinical classifications divided ARND into two subgroups; 1) individuals with severe dysfunction (CNS Rank 3) and 2) individuals with moderate dysfunction (CNS Rank 2). A recent MRI study confirmed SE/AE and ND/AE are distinct clinical subclassifications with clear evidence of CNS structural abnormality detectable by MRI volumetric analyses [9]. Importantly, the terms neither confirm nor rule-out the causal role of alcohol. In 2005, the Hoyme [19] and Canadian [37] guidelines also acknowledged the concern expressed by Aase and colleagues [13], but chose to continue the use of the term ARND. The Hoyme guidelines expressed the following reservations about the SE/AE and ND/AE terms introduced by the 4-Digit Code. They raised a number of important issues that warrant discussion.

"The Washington criteria place much emphasis on the encephalopathy and neurobehavioral disorder present among affected children. These 2 findings are not specifically defined and, as general terms, they are not unique to the prenatal effects of alcohol on fetal development. In addition, the family and genetic background of the child is not adequately integrated into the criteria. Because this highly structured system seems all-encompassing, there is the potential for over-diagnosis of alcohol-related disabilities; any child with a disability who has been exposed to

alcohol prenatally can be assigned a diagnostic classification easily, even if the cause of the disability is genetic" (p. 41) [19].

To clarify, the 4-Digit Code cannot over-diagnose "alcohol-related" disabilities because the only "alcohol-related" diagnoses the 4-Digit Code generates are FAS and Partial FAS. The potential to over-diagnosis alcohol-related disabilities occurs with the use of the term Alcohol-Related Neurodevelopmental Disorder. The 4-Digit Code is the only FASD guideline that does not use this term. The 4-Digit Code does assign a diagnostic classification to all individuals who present with a disability. The classification reflects their disability; their *outcome* per se (e.g., FAS, PFAS, Static Encephalopathy, Neurobehavioral Disorder, etc). For example, if the individual presented with moderate impairment in memory and executive function, their disability would be classified as Neurodevelopmental Disorder. All children with or without a disability also have their prenatal alcohol exposure status reported. Their exposure is reported separate from their disability using the following naming convention: "disability/exposure" (eg., FAS / Alcohol Exposed, FAS / Alcohol Exposure Unknown, Neurobehavioral Disorder/ Confirmed Absence of Alcohol Exposure; No Sentinel Physical Findings or CNS Abnormalities Detected/Alcohol Exposed, etc). This naming convention neither implies nor rules-out a causal association between the outcome and the exposure in an individual patient. Hoyme and colleagues are correct in stating that static encephalopathy and neurobehavioral disorder are not unique to the prenatal effects of alcohol on fetal development. The same holds true for the neurodevelopmental disorder referenced in ARND. This is why it is so important that the nomenclature not assert the outcomes are unique (related to) the alcohol exposure. The use of a nomenclature that reports outcome separate from exposure is perhaps one of the most important features and strengths of the 4-Digit Code that distinguishes it from all other FASD diagnostic guidelines.

The 4-Digit Code was developed under the premise that a diagnosis should be based on verifiable facts, not supposition. The diagnostic nomenclature used by the 4-Digit Code reflects this. Growth deficiency and CNS damage/dysfunction are not specific to (caused only by) prenatal alcohol exposure. When an individual presents with prenatal alcohol exposure and CNS damage/ dysfunction, but does not have the FAS facial phenotype, the damage/dysfunction may be entirely attributable to the prenatal alcohol exposure, partially attributable to the prenatal alcohol exposure, or unrelated to the prenatal alcohol exposure. It is important to remember that even when a diagnosis of full FAS is rendered, one cannot necessarily attribute ALL of the individual's disabilities to their alcohol exposure. To the extent that other adverse risk factors are present, they too can, and likely will, contribute to the overall constellation of outcomes.

Current medical technology has no ability to confirm or rule-out the etiologic role of alcohol in an *individual* patient. This does not prevent one from effectively moving forward. An accurate diagnosis and effective intervention can proceed without confirming alcohol caused the person's disability. Access to services should be based on a person's disability, not on what caused their disability. Prevention can also proceed without linking outcome to exposure in an individual patient. In fact, on an empirical level, valid identification of causal associations requires exposures and outcomes to be documented separately.

When an individual presents with CNS damage/dysfunction and prenatal alcohol exposure, the 4-Digit Code calls it what it is; Static Encephalopathy/Alcohol Exposed if the CNS damage/dysfunction is severe or Neurobehavioral Disorder/Alcohol Exposed if the CSN dysfunction is moderate. The medical definition of static encephalopathy is *"any significant abnormal condition of the structure or function of brain tissue that is neither progressing nor regressing*" [56]. Including the phrase "Alcohol Exposed" in the diagnostic name serves to alert clinical providers that the individual was exposed to a teratogen and therefore is at risk for underlying brain damage. Knowledge of this risk is important, because the presence of underlying brain damage should influence a clinician's approach to ongoing care and intervention.

Aase and colleagues [13] urged "*simple recording of the verifiable conclusions. . . . If prenatal alcohol exposure has taken place, but FAS cannot be substantiated, the exposure still should be indicated, and any nonspecific abnormalities or problems noted*." (p. 49) This is the approach taken by the 4-Digit Code. The clinical summary templates for SE/AE and ND/AE include the following statement: "The diagnosis of Static Encephalopathy/Alcohol Exposed (or Neurobehavioral Disorder/Alcohol Exposed) does not mean that alcohol is the cause of the problem. A number of other factors could be contributing to the present issues, such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth" [14, 38]. The 4-Digit Code also devotes a chapter and 4-Digit ranking system to documentation of other prenatal (including genetic) and postnatal exposures and events that frequently occur with prenatal alcohol exposure and likely contribute to the outcomes observed for individuals [38]. In fact, the vast majority of the 1,400 patients with prenatal alcohol exposure

diagnosed in the WA FAS DPN between 1993-2005 presented with multiple risk factors (93% were exposed to tobacco or illicit drugs in utero, 31% had no prenatal care, 36% had confirmed physical and/or sexual abuse, and 70% were in foster/ adoptive care) [50]. The impact of prenatal alcohol exposure is rarely if ever assessed in isolation from other risk factors.

The Hoyme guidelines [19] state, "FASD must always be a diagnosis of exclusion. Many genetic and malformation syndromes have some of the other clinical characteristics of FAS. If there is no indication of another genetic or malformation syndrome, then the revised IOM criteria can be applied to categorize a diagnosis within the FASD continuum" (quotes from pp. 45-46). Overlap between individual symptoms/anomalies is common throughout medicine. An astute clinician would not mistake FAS for William's syndrome simply because the two have some, but not all features in common. It is the constellation of features that distinguish the two syndromes. FAS is not a diagnosis of exclusion. Alcohol is a teratogen to all developing fetuses, including those with other genetic disorders or syndromes. It is worth noting that one child diagnosed with FAS in the WA FAS DPN also had Down syndrome. The child presented with growth deficiency below the 2nd percentile on a growth chart for children with Down syndrome. The child presented with the facial features of Down syndrome and FAS. The facial features of Down syndrome are distinct from the facial features of FAS. The two phenotypes were readily apparent and easily distinguished. The child presented with microcephaly (3 SDs below the mean for children with normal development, 1 SD below the mean for children with Down syndrome). The child presented with Bayley[57] Motor and Mental Index scores below 50; a level of developmental delay that can be observed in both Down syndrome and FAS. The birth mother was reported to have consumed alcohol daily throughout pregnancy. A FASD diagnostic team should consider alternative or co-occurring syndromic diagnoses and medical conditions at all times. The prevalence of other syndromes among 1,400 patients with prenatal alcohol exposure receiving a FASD diagnostic evaluation in a WA FAS DPN clinic is 1.8% [50]

Hoyme and colleagues [19] expressed concern that SE/AE and ND/AE are not specifically defined. The growth, face, CNS, and alcohol criteria are specifically defined for SE/AE and ND/AE (Table 3). The CNS functional criteria specify which functional domains may be impaired, how many must be impaired, and how severely (in SDs) each must be impaired. Most of the current guidelines (4-Digit Code [38], CDC [36], and Canadian [37] now provide this enhanced level of detail when defining the CNS functional criteria for their FAS, PFAS and ARND classifications.

ARBD: The term Alcohol-Related Birth Defects (ARBD) was introduced by the IOM [1] with the caveat that "*virtually every malformation has been described in some patient with FAS. The etiologic specificity of most of the anomalies to alcohol teratogenesis remains uncertain*". This statement remains true today. For this reason, the 4-Digit Code[38] and Canadian [37] Guidelines do not include ARBD as a diagnostic classification. The 4-Digit Code and Canadian guidelines require the reporting of all birth defects; they simply do not support labeling them as ARBD. The Hoyme [19] guidelines do include ARBD as a diagnostic classification, but require the FAS facial phenotype to be present. Inclusion of the FAS facial phenotype may help increase the chance that the birth defect may be related to the alcohol exposure, but only if the etiologic specificity of the guideline's FAS facial criteria is confirmed to be high.

Are Lip-Philtrum Guides Needed for each Race? All guidelines published subsequent to the 4-Digit Code have adopted the use of the University of Washington Lip-Philtrum Guides for measuring philtrum smoothness and upper lip thinness (Fig. 3). There are currently two Lip-Philtrum Guides; one normalized to Caucasians and one normalized to African Americans (Fig. 3). The Guides are purposely labeled Guide 1 and Guide 2, respectively, for they were created for use on more than just Caucasian and African American individuals. Guide 1 is intended for use on all races (or racial combinations) that indigenously have lips similar in thickness to Caucasians. Guide 2 is intended for use on all races (or racial combinations) that indigenously have lips similar in thickness to African Americans. The Guide that best matches the indigenous phenotype of the patient's race(s) should be used. It is essential that the patient's medical record document which Guide was used for their diagnostic evaluation.

While it may seem obligatory to create a Lip-Philtrum Guide for every race, there are two fundamental reasons why this is neither feasible nor clinically necessary. First, racial categories are more a social-political construct than scientific or anthropological classifications. Racial categories are not sufficiently case-defined to classify individuals accurately into discrete groups and a large portion of the population is multiracial. Finally, race rarely translates into one homogeneous phenotype. For example, there is tremendous phenotypic variability between American Indian tribes, thus creation of an "American Indian" Lip-Philtrum Guide would be clinically invalid. Second, the magnitude of difference that would differentiate lips of the same rank across more than two "racially-normed" guides would become imperceptibly small. The magnitude of difference would become clinically irrelevant and below the level of

accurate detection. To demonstrate this, look at how little difference there is between the Rank 5 lips on Guides 1 and 2 (Fig. 3). Now imagine the Rank 5 lip on a Lip-Philtrum Guide for a race that falls between Guides 1 and 2.

Can an accurate diagnosis be rendered at any age? The answer depends on the diagnosis and the guidelines. If a diagnostic classification requires standardized psychometric evidence of *higher level* dysfunction across multiple domains like language, memory, executive function, and/or cognition, then a patient must be old enough to engage in this higher level assessment (generally > 7 years old) to confirm or rule-out dysfunction. This is not to say a diagnostic evaluation should be postponed until after age 7. There is tremendous benefit to early diagnosis and intervention [17,48,58]. The 4-Digit Code explicitly states that a diagnosis rendered at an early age could change (upgrade to a more severe classification) as the child ages and higher level cognitive impairments emerge. As an example, if a 10 year old child presented with the following features (growth deficiency, the FAS facial phenotype, a normal head size, severe dysfunction in memory, executive function, and attention, and prenatal alcohol exposure), she would receive a diagnosis of FAS (4-Digit Code 4434). If she had received a diagnostic evaluation at 1 year of age, her severe functional impairments would not yet be apparent. They may only manifest as moderate developmental delays on a Bayley Scales of Infant Development [57], resulting in a 4-Digit Code of 4424 (sentinel physical findings, neurobehavioral disorder, alcohol exposed). Her true diagnosis would be FAS, but at 1 year of age, she would not be old enough to reveal the true magnitude of her CNS dysfunction. She benefits nonetheless from her early diagnosis in two ways: 1) she receives early intervention, and 2) her high risk status is documented in her medical record with recommendations to monitor her closely over time. If and when she presents with more severe CNS dysfunction, she would receive a FASD diagnostic re-evaluation to upgrade her diagnostic classification appropriately.

Can an accurate diagnosis be rendered in an adult? Yes. Adults often present with more complex life histories and competing risks (traumatic head injury, their own alcohol and drug abuse, and mental health problems). Confirmation of exposure can also be more challenging. But the same diagnostic criteria and interdisciplinary approach are utilized. The interdisciplinary team will need expertise in adult psychological assessment and knowledge of community services available to adults. While adults will not have benefited from early intervention, an accurate diagnosis will lead to a better understanding of their disability and improved access to disability assistance and services.

Before leaving this topic, one additional question regarding age and diagnosis is often asked: **Does the face of FAS change with age?** Literature from the 80's and 90's [59-61] would lead one to believe that infants and adults are less likely to present with the full FAS facial phenotype than school-aged children. But the data were largely anecdotal and focused on facial features that are no longer regarded as diagnostic of the FAS facial phenotype [20]. Data from 1,400 patients evaluated for FASD in the WA FAS DPN document just the opposite. The proportion of subjects who presented with the full FAS facial phenotype (Rank 4) by age group was as follows: birth to 3.9 yrs (14%), 4 to 16.9 years (7.7%), and 17 to 53 years (9.5%). The age group with the highest prevalence of the FAS facial phenotype was infants under one year of age (23%) [50]. It is certainly possible for the facial features to change with age. Although, in our experience, when change occurs it has always been quite subtle. In the event that facial features do change over time, most diagnostic guidelines address this by stating that the features may be present at *any* age. For example, if an adult presents with some, but not all of the FAS facial features, but childhood photos document the full FAS facial phenotype, then the adult would meet the full FAS facial criteria based on their childhood photos.

Overall, diagnostic evaluations for FASD can be conducted across the lifespan (newborn to adult). The diagnostic criteria do not change with age. The most accurate diagnosis can be rendered in childhood when the child is old enough to engage in all levels of assessment, but a diagnostic evaluation should not be postponed for this reason. Infants may require re-assessment. Adults present with unique challenges, but benefit nonetheless.

Validation of FASD Guidelines. It is imperative that the performance (reliability, accuracy, specificity, and validity) of diagnostic guidelines be confirmed through properly designed empirical studies [1]. A number of empirical studies have been published confirming the performance of the measurement tools, case-definitions, and diagnostic subclassifications used by the 4-Digit Code [7,9,10,14,16,20,21,39,50,62]. A recently completed MRI/fMRI/MRS study of children with FASD identified significant differences in neuropsychological outcomes [10], neurostructural outcomes [9], neuroactivation levels [21], and neurometabolite levels [63] between the FAS/PFAS, SE/AE and ND/AE clinical subgroups. Significant correlations were observed between size of brain regions and level of prenatal alcohol exposure, magnitude of FAS facial phenotype, and level of CNS dysfunction (Fig. 5). These findings confirm the 4-Digit Code produces three clinically distinct and increasingly more affected diagnostic subclassifications (FAS/PFAS, SE/AE, and ND/AE) under the umbrella of FASD.

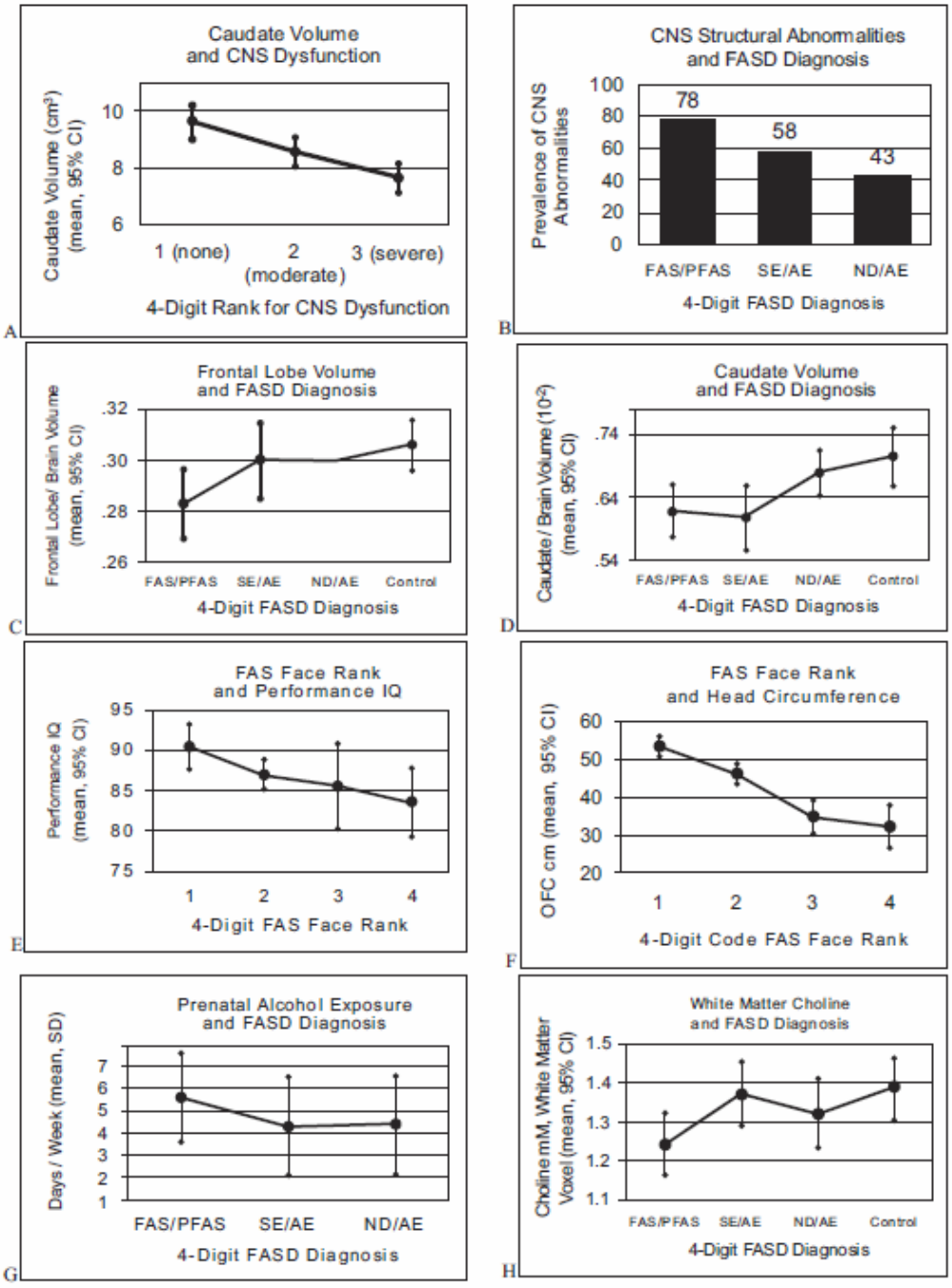


Figure 5: Examples of some of the many significant, empirical findings that serve to validate the performance of the FASD 4-Digit Diagnostic Code [9.10.50.63].

Patient Examples that Exemplify Key Contrasts between the Guidelines.

One practical method to assess the performance of the guidelines is to compare/contrast how they classify cases across the spectrum. Below are four hypothetical patient examples and the diagnostic classifications each would receive from the five most current FAS/D diagnostic guidelines [IOM [1], 4-Digit Code[38], Canadian[37], CDC[36], and Hoyme[19]]. These examples were selected to exemplify key contrasts between the guidelines. There are certainly many other examples that would result in identical diagnostic classifications across all five guidelines.

PATIENT EXAMPLE 1 (10 years old):

Growth: Hgt 10th percentile, wgt 95th percentile
Face: PFL 10th percentile;
Somewhat smooth philtrum, Rank 4;
Thick upper lip, Rank 1
CNS: OFC 10th percentile, FSIQ 120, No evidence of dysfunction.
Alcohol: Unknown

Diagnostic Classifications:

IOM: Unable to definitively classify. The IOM criteria are not sufficiently case-defined.
4-Digit Code: No sentinel physical findings or CNS abnormalities detected / Alcohol Unknown (4-Digit Code = 2212), Not FASD
Canadian: Not FASD
CDC: Not FAS
Hoyme: FAS / Alcohol Unknown

PATIENT EXAMPLE 2 (10 years old)

Growth: Hgt 2nd percentile, wgt 2nd percentile
Face: Small PFL, 2nd percentile,
Smooth philtrum, Rank 5,
Thin upper lip, Rank 5
CNS: OFC 30th percentile, No CNS structural/neurological abnormalities, FSIQ 50 (1st percentile). Severe dysfunction across all domains.
Alcohol: Intoxicated weekly throughout pregnancy

Diagnostic Classifications

IOM: Partial FAS? (This diagnostic classification is in question because the IOM growth deficiency criteria are not strictly met)
4-Digit Code: FAS/Alcohol Exposed (Code = 4434)
Canadian: FAS/Alcohol Exposed
CDC: FAS/Alcohol Exposed
Hoyme: Partial FAS/Alcohol Exposed

PATIENT EXAMPLE 3 (10 years old)

Growth: Hgt 50th percentile, wgt 50th percentile
Face: Normal PFL 50th percentile,
Normal philtrum Rank 2,
Normal upper lip Rank 2
CNS: OFC 50th percentile, No CNS structural/neurological abnormalities. ADHD, Significant memory impairment, All other domains of function within normal range.
Alcohol: One glass of wine nightly throughout pregnancy. No reports of binge drinking, intoxication, or problems with alcohol use.

Diagnostic Classifications:

IOM: Not FASD
4-Digit Code: Neurobehavioral Disorder / Alcohol Exposed (Code = 1123)
Canadian: Not FASD
CDC: Not FAS.
Hoyme: Not FASD

PATIENT EXAMPLE 4: (2 years old)

Growth: Hgt 1st percentile, wgt 1st percentile
Face: Small PFL 1st percentile,
Smooth philtrum, Rank 5,
Thin upper lip, Rank 5
CNS: OFC 1st percentile, Bayley Scales of Infant Development outcomes within low-normal range.
Alcohol: Intoxicated weekly throughout pregnancy

Diagnostic Classifications:
IOM: Partial FAS? (This diagnosis is in question because the IOM growth deficiency criteria are not strictly met)
4-Digit Code: FAS/Alcohol Exposed (Code = 4444)
Canadian: Not FASD
CDC: FAS/Alcohol Exposed
Hoyme: FAS/Alcohol Exposed

FUTURE DIRECTIONS

Without doubt, the one emerging arena that will have the greatest impact on the future of FASD diagnosis is brain imaging. All diagnostic guidelines include "evidence of abnormal brain structure (e.g., abnormal MRI, microcephaly)" as a key diagnostic criteria for FAS, PFAS, and ARND (or its equivalent). Detection of abnormal structure currently relies on radiologist review (visual inspection) of brain images. But MRI technology can now produce accurate measures of size/shape/and tissue composition of brain regions that provide far more sensitive measures of structural abnormality [9, 64-66]. For example, in a recently completed FASD MRI study, none of the 23 children with ND/AE were identified as having an abnormal MRI by radiologist review, yet 43% of the subjects had one or more brain regions, two or more standard deviations below the mean size observed in the healthy Control group using MRI volumetric analysis [9]. Does this mean 43% of these children now meet the diagnostic criteria for having an "abnormal MRI"? Not necessarily. Norms for the size of brain regions, by gender and age, must be established using large, representative, population-based samples, rather than small, convenient research control samples. The National Institutes of Health MRI Study of Normal Brain Development [67, 68] is a landmark study that is documenting structural brain development and behavior longitudinally from birth to young adulthood in a large population-based sample of healthy children targeted to the United States 2000 census distribution. Thus, we will soon have "normal growth charts" for the size of brain regions, much like we have normal growth charts for height, weight, and head circumference. If microcephaly meets the FASD criteria for a structural brain abnormality, should a significantly small frontal lobe or caudate volume meet the criteria? The answer will likely depend, in part, on how size correlates with function. Decreasing head circumference is correlated with increasing severity of dysfunction [9, 69]. A rapidly growing literature documents similar correlations exist between regional brain volumes and function [9, 65,70] (Fig. 5A). If brain imaging technology is adopted into the FASD diagnostic evaluation process, the prevalence of FAS/D will increase, simply by virtue of increased sensitivity to detect structural brain abnormality.

SUMMARY REMARKS

1. An FASD diagnostic evaluation is most accurately conducted by an interdisciplinary team.

2. The field should strive to adopt a single set of diagnostic guidelines for FASD.

3. Guidelines should undergo rigorous assessment of their accuracy, reliability, specificity, and validity to confirm their high performance, preferably before their release.

4. Use of the terms ARND and ARBD, like FAE, should be discontinued. They should be replaced by terminology that does not imply or rule-out a causal association between outcome and exposure in an individual patient.

5. Exposure and outcome should be assessed and reported separately.

6. The FAS facial phenotype must by highly specific to prenatal alcohol exposure and FAS to render a valid diagnosis of FAS, especially in the absence of a confirmed prenatal alcohol exposure. Specificity must be confirmed through properly designed empirical studies.

7. Diagnostic criteria should not require 'excessive' levels of alcohol exposure because a safe level of exposure has not been confirmed for all individuals and the accuracy of an exposure history can never be verified.

8. The report summarizing the outcome of an FASD diagnostic evaluation should report the FASD diagnostic classification, which diagnostic guidelines were used, all data required to confirm the diagnostic criteria were met and all recommendations documented.

9. Access to intervention services should be based on a patient's disability, not on what caused their disability.

CONCLUSIONS

Accurate, reliable, diagnoses across the full continuum of FASD have been available to families and clinicians for over a decade. As medical technology and our understanding of FASD advance, so must our diagnostic methods and tools. It is imperative that advancements in diagnostic methods be guided by an evidence base of rigorously designed, implemented, and peer-reviewed research. When a diagnosis under the umbrella of FASD is made, two individuals are affected directly; the child and the birth mother. The consequences of an incorrect diagnosis for both mother and child must be considered carefully. Diagnostic guidelines should guide professionals in rendering an accurate medical diagnosis. A diagnosis reflects the condition of a patient; however, because a diagnosis serves many purposes (eg, treatment, prevention, communication among specialists, and qualification for services), the process of rendering a diagnosis can sometimes be influenced by those different purposes. The only diagnosis that serves all purposes most effectively is a correct diagnosis. Access to services should be based on an individual's disabilities and not on what caused their disabilities. Therefore, services should be available for individuals across the full continuum of FASD and not just those with FAS.

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Another perspective on 'The effect of different alcohol drinking patterns in early to mid pregnancy on the child's intelligence, attention, and executive function'

Sir,

It has been suggested in a series of papers published on 20 June 2012 in *BJOG*[1–5] that low and moderate weekly alcohol consumption in early pregnancy is not associated with adverse neuropsychological effects in children aged 5 years. The authors of the papers state that it remains the most conservative advice for women to abstain from alcohol during pregnancy; however, small amounts may not present a serious concern.

The researchers studied 870 preschool children whose mothers reported drinking during pregnancy and compared them with 758 preschool children whose mothers reported not drinking during pregnancy. They measured the children's IQ and attention levels at the age of 5 years. Children exposed prenatally to 1–8 drinks per week had the same IQ and attention levels as children with no exposure to alcohol.

We contend that the reason the children in this study did not appear to be harmed by the alcohol is because the children were too young to measure the full impact alcohol may have had on their brains. At 5 years of age, the brain is still developing. A 5-year-old's brain is not developed sufficiently to perform complex tasks, such as remembering and following multiple instructions, writing a report, communicating abstract ideas effectively or exercising good judgment. Over 30 years of research on fetal alcohol syndrome (FAS) confirms that alcohol has its greatest impact on complex brain functions.[6] This is why children exposed to and damaged by prenatal alcohol exposure do deceptively well in their preschool years. The full impact of their alcohol exposure will not be evident until their adolescent years.

Please consider the following statistics based on 2600 children who received a diagnostic evaluation for FAS in the Washington State FAS Diagnostic & Prevention Network clinics over the past 18 years.

- One of every seven children diagnosed with FAS (the most severe outcome caused by prenatal alcohol exposure) had a reported exposure of 1–8 drinks per week. (The Danish studies did not conduct FAS diagnostic evaluations on the children.)
- One-half of the children with FAS had developmental scores in the normal range as preschoolers. However, all had severe brain dysfunction confirmed by the age of 10 years. (The Danish studies only assessed preschoolers.)
- Only 10% of the children with FAS had attention problems by the age of 5 years; 60% had attention problems by the age of 10 years. (The Danish studies only assessed attention at the age of 5 years.)
- Only 30% of the children with FAS had an IQ below normal. However, 100% had severe dysfunction in other areas, such as language, memory and activity level. (The Danish studies did not assess these areas.)

Although the science may be complicated and studies sometimes yield conflicting messages, the public health message is simple: to have the *healthiest baby possible*, women should not drink alcohol when trying to conceive and during pregnancy. When a pregnant woman drinks, her child is at risk. If she drinks heavily, her child is at higher risk. ■

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Parenting Stress and Sensory Processing: Children With Fetal Alcohol Spectrum Disorders

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key words: sensory processing, prenatal alcohol exposure, school-aged children

ABSTRACT

Sensory processing differences are reported in a high proportion of children with fetal alcohol spectrum disorders (FASD), but how these problems impact caregiver burden has not been investigated. Linear regression was used to examine the association between parenting stress and problems in sensory processing, along with other child and family characteristics, among 52 children aged 5 to 12 years with FASD. Participants also had clinically significant problem behaviors. Higher levels of child-related parenting stress were moderately correlated with more parent-reported sensory processing problems (r = *-.60). Regression findings revealed that parent-reported problems in children's behavior regulation, an aspect of executive function, and sensory processing deficits were the strongest predictors of child-related parenting stress, together accounting for 62% of variance. Children's sensory processing deficits and executive function impairments affect the parent–child system and should be central considerations when developing family-centered supports for children with FASD.*

Prenatal alcohol exposure can result in a continuum of neurodevelopmental disabilities known collectively as fetal alcohol spectrum disorders (FASD; Bertrand et al., 2004). Children with FASD demonstrate a range of neurobehavioral deficits often including sensory processing problems that can interfere with successful occupational performance and participation. Using validated caregiver report measures, high rates of sensory processing problems (80% to 88%) have been reported among clinical samples of children with FASD (Carr, Agnihotri, & Keightley, 2010; Franklin, Deitz, Jirikowic, & Astley, 2008; Jirikowic, Kartin, & Olson, 2008). Poor sensory processing has shown moderate associations with child characteristics including increased problem behaviors (Franklin et al., 2008) and poorer adaptive skills (Carr et al., 2010; Jirikowic et al., 2008) among school-aged children with FASD. However, the relationships between children's sensory processing difficulties and attitudes important to parenting success have not yet been examined in this clinical population, despite their importance for informing intervention.

It is well established that caregivers raising children with many types of neurodevelopmental disabilities report elevated levels of parenting stress (Estes et al., 2009; Hauser-Cram et al., 2001; Johnston et al., 2003; Webster, Majnemer, Platt, & Shevell, 2008). Over the long term, parenting stress may have

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deleterious effects on family relationships, maternal health and quality of life, and child behavioral outcomes in families raising children with developmental disabilities (Eisenhower, Baker, & Blacher, 2009; Hauser-Cram et al., 2001). Indeed, parenting stress is an overarching concern for caregivers raising children born prenatally exposed to alcohol and high rates of clinically elevated parenting stress have been found among caregivers raising school-aged children with FASD (Olson, Oti, Gelo, & Beck, 2009; Paley, O'Connor, Frankel, & Marquardt, 2006; Paley, O'Connor, Kogan, & Findlay, 2005).

In the effort to understand sources of parenting stress, common characteristics among children with developmental disabilities have been explored, such as intellectual level, magnitude of problem behaviors, and decrements in adaptive function. Important contributors differ across clinical populations. For example, among preschool children with autism spectrum disorders or developmental delays, the magnitude of child problem behaviors was the most significant predictor of parenting stress, whereas child intellectual level and adaptive function were not salient predictors (Estes et al., 2009). In contrast, lower child cognitive levels and poorer adaptive function were both associated with greater parenting stress among biologically vulnerable toddlers with varying developmental risk factors, including prenatal alcohol exposure, although problem behaviors were not considered (Secco et al., 2006).

Interestingly, sensory processing deficits have rarely been considered as a contributor to parenting stress in these populations. Yet, the behavioral sequelae that stem from sensory processing impairments (i.e., the need to avoid or seek sensation in ways that are different from children with typical development) may be stressful for parents. This is because associated behaviors can prolong or impede household routines, impact family participation in community activities or social events, and hinder the development of mutually positive and satisfying parent–child relationships (Dunn, 2007). To our knowledge only one study to date has systematically examined sensory processing and parenting stress. Epstein, Saltzman-Benaiah, O'Hare, Goll, and Tuck (2008) investigated the relationships between parenting stress and child characteristics in 39 children aged 5 to 12 years with Asperger syndrome. Findings revealed a significant, moderately high relationship between maternally reported sensory processing behaviors as measured by the Short Sensory Profile (SSP; Dunn, 1999) and higher levels of parenting stress (r = -.56; $p < .007$) on the Parenting Stress Index (PSI; Abidin, 1995) short form.

When challenging child characteristics co-occur with adverse parent and family factors, parenting stress can be compounded. Parent characteristics, family context, and life stress events have all been identified as important facets affecting the parent–child system (Abidin, 1995). Ecological factors that have been associated with parenting stress include the availability of parenting and social supports, income level and socioeconomic status, family structure, and maternal depression (Abidin, 1995; Guralnick, Hammond, Neville, & Connor, 2008; Johnston et al., 2003; Secco et al., 2006). The significance and relative contributions of each of these ecological factors vary widely among the populations studied. For families dealing with substance abuse issues, such as birth parents, these ecological risks may often be multiple and pervasive, which render factors such as family resources, social support, and overall life stress especially salient considerations for these families (Astley, Bailey, Talbot, & Clarren, 2000; Nair, Schuler, Black, Kettinger, & Harrington, 2003).

To date, two studies have examined the associations between parenting stress and maternal, family, and child factors among caregivers of children affected by prenatal alcohol exposure. Paley et al. (2005) used path analysis to explore the sources of stress among 42 high-risk mothers of preschool children with high levels of prenatal alcohol exposure. Child factors (e.g., externalizing behavior problems and intellectual level) and ecological factors (e.g., socioeconomic status, current maternal alcohol use, and available parent support resources) were analyzed. The model revealed that greater child externalizing behavior problems and fewer parent support resources best explained maternal stress above and beyond other child and family factors. Contributors to parenting stress were also examined among children with diagnoses across the fetal alcohol spectrum among a sample of 100 parent–child dyads (Paley et al., 2006). Greater child-related parenting stress, assessed using the PSI (Abidin, 1995), a standardized parenting stress questionnaire, was associated with parent reports of greater child externalizing and internalizing behavior problems, decreased adaptive function, and increased level of executive function impairment. Notably, child executive function impairment, measured by the overall General Executive Composite score on the Behavior Rating Inventory of Executive Function-Parent Form (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000) was the strongest predictor of child-related parenting stress in this analysis.

Although it is clear that parents of children with FASD are highly stressed by characteristics of their children and face other psychosocial risks, this clinical population is not yet well understood and interventions are still in the early stages of development.

Given the high rates of sensory processing problems previously reported in this group of children with neurodevelopmental disabilities, this study aimed to determine whether poor sensory processing, in combination with other salient child and family characteristics, is a significant source of parenting stress among caregivers raising children with FASD.

Methods

Research Design

This was a descriptive study of 52 children, aged 5 to 12 years, with systematically diagnosed conditions falling under the umbrella term of FASD, all with clinical concerning behavior problems, who were enrolled in a two-group randomized control trial designed as an initial efficacy test of the Families Moving Forward (FMF) Program intervention model (see Bertrand & Interventions for Children With Fetal Alcohol Spectrum Disorders Research Consortium, 2009 [Study #5]; Olson et al., 2009). The FMF Program is a caregiver-focused behavioral consultation intervention that aimed to reduce challenging child behaviors and, ultimately, to enhance caregiving attitudes and parenting practices, meet family needs, promote caregiver self-care, and provide useful linkages to community services. The overall study was approved by the University of Washington Human Subjects Division. Data for the current descriptive study came from the baseline assessment, which took place prior to participant randomization or any intervention.

Participants

Children were recruited from the University of Washington Fetal Alcohol Syndrome Diagnostic and Prevention Network (FAS DPN) clinical database, which at the time of the study contained more than 1,500 patient records with patient consent and human subjects approval for research recruitment. Participants in the FAS DPN database represent a clinical population of individuals with confirmed prenatal alcohol exposure systematically diagnosed by an interdisciplinary team (Astley & Clarren, 2000; Clarren, Olson, Clarren, & Astley, 2000) using the FASD 4-Digit Diagnostic Code (Astley, 2004).

The 4-Digit Diagnostic Code has been demonstrated to be a sensitive and reliable method to diagnose fetal alcohol syndrome (FAS) and other conditions on the fetal alcohol spectrum (Astley, 2004, Astley et al., 2009a, 2009b). The four digits of the code reflect the magnitude of expression of the key diagnostic features of FASD: (1) growth deficiency; (2) characteristic facial phenotype; (3) central nervous system damage/dysfunction; and (4) maternal alcohol consumption during pregnancy. The magnitude of expression of each feature is ranked independently on a 4-point Likert scale with "1" reflecting complete absence of the FAS feature and "4" reflecting a strong "classic" presence of the FAS feature. The 4-Digit Codes that fall under the umbrella of FASD can be subclassified into one of four unique clinical diagnostic categories from more severe to less severe: (1) FAS, characterized by growth deficiency, facial anomalies, and severe central nervous system dysfunction, (2) partial FAS/alcohol-exposed (without growth deficiency), (3) static encephalopathy/alcohol-exposed (severe central nervous system dysfunction without the FAS facial features), and (4) neurobehavioral disorder/alcohol-exposed (mild to moderate central nervous system dysfunction without the FAS facial features) (Astley, 2004).

Procedures

Following enrollment and informed consent, all children received a comprehensive baseline neurodevelopmental assessment and primary caregivers were interviewed and asked to complete standardized questionnaires during a research laboratory visit. Caregiver interviews were conducted by trained psychometrists with an educational background in social or human services. Child assessments were completed by psychology graduate students with advanced training in child psychopathology and psychometric assessment. All testers were trained on the test administration and scoring via pilot testing, achieving acceptable interrater reliability at baseline and midway through the testing period. Testers were aware that the participants had a diagnosis on the fetal alcohol spectrum, but had no knowledge of prior or current test results. Testers were not involved in the intervention.

The child assessment profiled each child's neurodevelopmental function, including sensory processing, and evaluated child strengths, social skills, behavior problems, and cognitive/linguistic abilities including executive function. Caregiver needs and attitudes, including parenting stress, were assessed, as were parenting practices, family characteristics, child life experiences, and demographics. The assessments were typically done as one visit (4.5 hours) with several breaks and refreshment during the session. A few children, usually those who were younger, were seen for two sessions to minimize fatigue. Adaptive behavior data were gathered via a semi-structured interview during phone calls to the primary caregiver at a time convenient to the family following the baseline laboratory visit.

Instrumentation

PSI, Long Form (Abidin, 1995). This standardized questionnaire evaluates parenting stress for parents of

children from 1 month to 12 years of age. Scores in each domain at or above the 85th percentile suggest clinically elevated stress. The Child Domain (PSI Child) taps current child characteristics that may be major factors contributing to stress in the overall child–parent system. The Parent Domain (PSI Parent) taps current caregiver factors that may contribute to overall stress and dysfunction in the parent–child system. The Life Stress Domain provides an indicator of the amount of stress a caregiver has experienced during the past 12 months outside the parent–child system (e.g., divorce or changes in income). Internal consistency is reported for the Child Domain (α = .70 to.83) and Parent Domain (α = .70 to .84). Test–retest reliability coefficients across three different studies are reported for the Child Domain (r = .63 to .82) and Parent Domain (r =. 75 to .91). Construct and predictive validity are reported across child and parent populations.

SSP (Dunn, 1999). The SSP is a standardized parent questionnaire that examines sensory processing behaviors for children aged 3 through 10 years. The SSP measures the following domains of sensory processing: (1) Tactile Sensitivity; (2) Taste/Smell Sensitivity; (3) Movement Sensitivity; (4) Underresponsive/Seeks Sensation; (5) Auditory Filtering; (6) Low Energy/Weak; and (7) Visual/Auditory Sensitivity. A total score is generated from each domain and lower scores indicate that problem behaviors occur more frequently. Raw scores are also classified into categories of typical performance (scores > -1.0 standard deviation from the mean), probable difference (scores -1.0 to -2.0 below the mean), and definite difference (scores < -2.0 from the mean). The SSP has good internal reliability (α = .70 to .90). Behavioral outcomes on the SSP are consistent with physiological outcomes in children with and without sensory modulation disorders (i.e., children with lower scores on the SSP show abnormal electrodermal skin response to sensory stimuli), supporting the SSP construct validity (McIntosh, Miller, Shyu, & Hagerman, 1999).

BRIEF-Parent Form (Gioia et al., 2000). The BRIEF is a standardized caregiver report of executive functioning behaviors for children aged 5 to 18 years. The BRIEF has two indices, the Behavioral Regulation Index (BRIEF BRI) and the Metacognitive Index (BRIEF MCI), which combine to create the overall General Executive Composite score. The BRI and MCI were the variables of interest for this study, with higher T scores indicating more problematic behaviors. The BRIEF BRI and MCI have good test–retest reliability (r = .84; r = .88) and internal consistency (α = .96), respectively. The BRIEF has evidence of good convergent validity with other measures of inattention, learning, and impulsivity.

ASEBA Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2000, 2001). Problem behaviors were measured using the age-appropriate version of the CBCL. These are standardized parent questionnaires used to assess behavioral/emotional problems that have occurred during the past 6 months. The Total Problem T score was the variable of interest for this study. Higher T scores reflect the presence of more problem behaviors. Test–retest reliabilities ranged from r = .82 to .94 and internal consistency reliabilities ranged from α = .82 to .97. For both age-level versions of the CBCL, evidence for content validity, criterion-related validity, and construct validity is provided.

Vineland Adaptive Behavior Scales, Interview Edition, Survey Form, First Edition (VABS; Sparrow, Balla, & Cicchetti, 1984). The VABS is a semi-structured interview that examines a caregiver's assessment of the child's adaptive function in four domains: (1) communication; (2) daily living skills; (3) socialization; and (4) motor skills (for children younger than 6 years). The Adaptive Behavior Composite (VABS ABC), the study variable of interest, is a standard score derived from the component domain standard scores. There is extensive data to support construct and concurrent validity, and the VABS ABC has excellent test–retest reliability (intraclass correlation coefficient = .99) and interrater reliability (intraclass correlation coefficient = .98).

Kaufman Brief Intelligence Test (KBIT; Kaufman & Kaufman, 1990). The KBIT provides an estimate of verbal and nonverbal intellectual status for individuals aged 4 to 90 years. Results yield three scores: Verbal IQ, Nonverbal IQ, and an overall composite IQ. The internal consistency reliability for the IQ composite for 4 to 19 year olds is α = .92. Test–retest reliability is r = .90. The Verbal IQ score was the variable of interest for this study because the composite IQ score could not be calculated for four children with significantly different scores between the verbal and nonverbal scales.

Data Analysis

Child and family characteristics were summarized using means, standard deviations, range of values, and proportions. The relationships between PSI outcomes and salient child and family characteristics were explored statistically prior to the regression analysis (e.g., chi-square for categorical variables and Pearson correlation coefficients for continuous variables). Child sociodemographic variables examined were age, gender, number of stressful life events, and diagnosis on the fetal alcohol spectrum. Child characteristics examined were sensory processing (SSP Total raw score), IQ (KBIT Verbal IQ standard

Table 1
Child and Caregiver Sociodemographic Characteristics (*N* = 52)

Variables	No. (%)[a]
Child gender (%)	
Male	27 (51.9)
Female	25 (48.1)
Child age (y)	
M (*SD*)	8.53 (2.03)
Low/high	5.0–11.85
Child race/ethnicity (%)	
White/Non-Hispanic	26 (50.0)
White/Hispanic	2 (3.8)
African American	4 (7.7)
Native Ancestry	2 (3.8)
Mixed Ethnicity	18 (34.6)
Primary caregiver type (%)	
Biological parent(s)	6 (11.5)
Biological grandparent	6 (11.5)
Adoptive parent	25 (48.0)
Foster parent	8 (15.4)
Legal guardian	2 (3.8)
Other (relative, stepmother)	5 (9.6)
Primary caregiver married/living with partner (%)	39 (75)
No. of children in current home	
M (*SD*)	2.67 (1.28)
Low/high	(1–7)
No. of significant earlier stresses (child)	
M (*SD*)	5.19 (2.28)
Low/high	(0–9)
Diagnosis (%)[b]	
FAS or partial FAS	10 (19.2)
Static encephalopathy/alcohol-exposed	21 (40.4)
Neurobehavioral disorder/alcohol-exposed	21 (40.4)
Annual household income	
< $15,0000	6 (11.5)
$16,000–39,000	8 (15.4)
$40,000–59,000	15 (28.9)
$60,000–79,000	8 (15.4)
$80,000–99,000	7 (13.5)
> $100,000	8 (15.4)

M = mean; SD = standard deviation; FAS = fetal alcohol syndrome.
[a]*Percentages may not total 100% due to rounding.*
[b]*See Astley (2004) for a full description of the 4-Digit Diagnostic Code diagnoses.*

score), executive function (BRIEF MCI and BRIEF BRI T scores), problem behaviors (CBCL Total Problems T score), and adaptive function (VABS ABC standard score). Family characteristics considered were caregiver marital status, caregiver type, gross annual income, and number of children in the home. Variables that were statistically significant were then entered as independent variables into a stepwise linear regression to examine their relationship with the PSI. The stepwise F to enter in the regression analysis was set at a *p* value of less than .05 and F to remove was set at a *p* value of less than .10. Data were analyzed using Statistical Package for Social Sciences Version 18.0 software (SPSS, Inc., Chicago, IL).

Results

Sociodemographic data are presented in Table 1. This was a diverse sample of school-aged children with FASD and their caregivers from the standpoint of variables such as child ethnicity, gender, and socioeconomic status. The proportion of children in the care of their biological parent(s) in the study sample was small (11.5%); however, the proportion of children in the care of their biological parent(s) is also small (30%) in the FAS DPN clinical population from which they were drawn (Astley, 2010). The sample was representative of the larger clinical population in terms of gender and white/non-white participants, but this sample included a higher percentage (48%) of adoptive parents and caregivers reporting higher gross annual income levels.

Descriptive statistics for measures of parenting stress and child characteristics are presented in Table 2. A striking 92% of parents reported clinically elevated levels of stress (raw scores > 85th percentile) on the PSI Child Domain, compared to only 21% and 8% of the sample reporting clinically elevated stress on the Parent Domain and Life Stress Domain, respectively. Because most parents did not demonstrate clinically elevated levels of stress in the Parent Domain or Life Stress Domain, the regression analysis focused only on child-related parenting stress using the PSI Child as the dependent variable.

Regarding child characteristics, this sample of children with FASD displayed estimated intellectual level in the average range, coupled with well-below average adaptive function. A high proportion of the children had sensory processing difficulties. On the SSP, 83% of the children were categorized with "definite differences," 12% had "probable differences," and only 5% had typical performance. The children also showed high levels of clinically significant behavior problems and clinically concerning executive

Table 2
Descriptive Statistics for Child Measures and Parenting Stress

Measures	*M* (*SD*)	Low/High
Child Function		
SSP[a] Total Score	126.8 (18.9)	73–176
VABS ABC Composite[b]	66.0 (11.2)	42–93
CBCL Total Problems[c]	70.9 (6.0)	51–86
BRIEF-BRI[d]	75.2 (9.0)	54–95
BRIEF-MCI[e]	71.3 (7.3)	53–87
KBIT Verbal[f]	94.4 (12.9)	75–130
Parenting Stress		
PSI[g] Child Domain	141.5 (19.1)	94–183
PSI[g] Parent Domain	126.6 (21.1)	85–182
PSI[g] Life Stress Domain	7.8 (6.3)	0–23

M = mean; SD = standard deviation.
[a]Short Sensory Profile (SSP; raw score).
[b]Vineland Adaptive Behavior Scales (VABS ABC standard score; M = *100;* SD = *15).*
[c]Child Behavior Checklist (CBCL T score; M = *50;* SD = *10).*
[d]Behavior Rating Inventory of Executive Function Behavior Regulation Index (BRIEF-BRI; T score; M = *50;* SD = *10).*
[e]Behavior Rating Inventory of Executive Function Metacognitive Index (BRIEF-MCI; T score M = *50;* SD = *10).*
[f]Kaufman Brief Intelligence Test (KBIT Verbal; standard Score; M = *100;* SD = *15).*
[g]Parenting Stress Index (PSI; raw score).

function impairments in the domains of behavioral regulation and metacognition.

No significant correlations were found between the PSI Child Domain score and the child sociodemographic characteristics of age, gender, number of stressful life events, and diagnosis on the fetal alcohol spectrum or the family characteristics of caregiver marital status, caregiver type, gross annual income, and number of children in the home. Four measures of child neurobehavioral characteristics (BRIEF BRI, SSP, CBCL Total Problems, and VABS ABC) were significantly correlated with child-related parenting stress (PSI Child; see Table 3) and with each other. These four child neurobehavioral characteristics were entered into the regression equation as independent variables. Table 4 presents the regression analysis examining the relationship between these four child characteristics and the dependent variable of caregiver-reported parenting stress on the PSI Child Domain.

The overall model predicting child-related parenting stress was significant, at $F = 39.60$, $p < .001$. In this model, the BRIEF BRI and SSP Total score together explained 62% of variance in child-related parenting stress. The BRIEF BRI was the strongest predictor of parenting stress, whereas the SSP accounted for an additional R^2 change of .12.

Table 3
Significant Correlations Between Child-Related Parenting Stress and Child Characteristics

Measure	1	2	3	4	5
SSP[a]	–	.30*	-.57**	-.39**	-.60**
VABS[b]	–	–	-.41**	-.45**	-.40**
CBCL[c]	–	–	–	.63**	.63**
BRIEF BRI[d]	–	–	–	–	.70**
PSI Child[e]	–	–	–	–	–

[a]Short Sensory Profile (SSP; raw score).
[b]Vineland Adaptive Behavior Scales (VABS ABC; standard score; M = *100;* SD = *15).*
[c]Child Behavior Checklist (CBCL; T score; M = *50;* SD = *10).*
[d]Behavior Rating Inventory of Executive Function Behavior Regulation Index (BRIEF-BRI) (T score; M = *50;* SD = *10).*
[e]Parenting Stress Index Child Domain (PSI Child; raw score).
**p < .05, two-tailed. **p < .01, two-tailed.*

Discussion

Child-related parenting stress occurred frequently and at high levels within the diverse group of caregivers raising children with FASD. To understand sources of stress in this clinical population, sensory processing behaviors were considered along with more commonly explored child and family characteristics associated with caregiving stress. Sensory processing differences together with the powerful variable of parent-reported problems in children's behavioral regulation (an aspect of executive function) were the strongest predictors of child-related stress in this sample of caregivers raising children with FASD. Assessment of differences in children's sensory processing captured variance beyond that explained by executive function impairments alone. Thus, for children with FASD with challenging behavior problems, difficulty modulating sensation, as perceived by their caregivers, had a significant and independent effect on daily parenting stress. This effect has important clinical implications because sensory processing knowledge can provide an additional and unique perspective to add to our understanding of parenting challenges reported by caregivers of children with FASD.

Consistent with previous findings among children with FASD (Paley et al., 2006), a strong association between child-related parenting stress and executive function impairment was seen. Results from the current study expand what is known about this common characteristic of children affected by prenatal alcohol exposure and its impact on caregivers (Kodituwakku, 2009; Vaurio, Riley & Mattson, 2008). The BRIEF BRI, assessing a child's inhibitory control and ability to shift cognitive set (e.g., make transitions, alternate

Table 4
Stepwise Regression Analysis: Child Characteristics Contributing Variability to Child-Related Parenting Stress (Parenting Stress Index: Child Domain)

	β	B (SE)	R^2(adjusted R^2)	Δ R^2
Step 1				
Constant	–	28.52 (16.21)	.50 (.49)	.50
Executive Function: Behavior Regulation (BRIEF-BRI)[a]	.71	1.50 (.21)	–	–
Step 2				
Constant	–	101.03 (23.25)	.62 (.61)	.12
Executive Function: Behavior Regulation	.56	1.19 (.20)	–	–
Sensory Processing (SSP)[b]	-.38	-.39 (.10)	–	–

Note. *Four measures of child characteristics were made available for stepwise entry into the regression equation (BRIEF BRI, SSP, CBCL Total Problems, and VABS ABC).*
[a]*Behavior Rating Inventory of Executive Function, Behavioral Regulation Index (BRIEF BRI).*
[b]*Short Sensory Profile (SSP).*

attention) and modulate emotions was clinically elevated and strongly and significantly correlated with parenting stress. In contrast, the BRIEF-MCI, which taps behaviors representing a child's ability to initiate, plan, and organize, and use working memory for problem-solving, was not significantly correlated with child-related parenting stress. Decrement in children's behavior regulation skills was the aspect of executive function that contributed most to child-related caregiver burden and stress.

Interestingly, measures of the children's level of adaptive function (VABS ABC) and behavior problems (CBCL Total Problems) did not explain additional variance in the regression model once executive function and sensory processing impairments were taken into account. This was most likely due to the strong intercorrelations between these four measures of child behavior (BRIEF-BRI, SSP, VABS-ABC, and CBCL Total Problems). It is also possible that with the moderate sample size of this study, the unique contributions of adaptive behavior and problem behavior to parenting stress were not detected in the model. Indeed, this sample of children demonstrated significant decrements in age-appropriate self-care, socialization, and communication skills and had clinically concerning problem behaviors. Previous studies of families raising children with prenatal alcohol exposure or FASD substantiate these adaptive skill and behavioral challenges (Jirikowic, Gelo, & Astley, 2010) and their relationship with more caregiver stress (Paley et al., 2005, 2006).

Conceptually, a neurodevelopmental viewpoint that interprets maladaptive behaviors as underlying "brain-based" difficulties offers insight into these strong interrelationships (Olson, Jirikowic, Kartin, & Astley, 2007; Olson & Montague, 2011). The relevant "brain-based" difficulties for children with FASD that stress parents appear to be challenges in both the child's sensory processing and executive function. Impairments in these neurodevelopmental domains may underlie many of the challenging, dysregulated behaviors that significantly compromise adaptive function in children with FASD and make parenting so difficult.

The pattern of caregiver stress reported in this study differs from earlier investigation of the sources of parenting stress among families raising children with FASD. The most significant issue for the current sample was child-related stress. This sample of relatively low-risk caregivers, even though a diverse group of birth, kinship, and foster and adoptive parents, did not on average report elevated levels of stress regarding the parenting role or overall life stress on the PSI. Demographics may explain why these findings differ from earlier studies of this issue. A high percentage of families in the current study were two-caregiver families, who were educated beyond high school graduation and reported low moderate to high income levels. Unlike the high-risk families examined earlier by Paley et al. (2006), where family resources were a significant predictor of stress in both parent and child domains, the environmental factors expected to be related to parenting stress (i.e., marital status, family type, and income) did not show significant associations. One exception was the number of children in the household, which was significantly associated with parenting role-related stress (-.30; $p < .05$). Thus, most families in the current study presumably had adequate family resources to meet basic needs and access social support.

Limitations

Although this study used a systematically diagnosed sample of children with FASD, the children in this sample were recruited for an intervention study

and selected because they presented with clinically concerning behavior problems. Thus, the sample may not be representative of all children affected by prenatal alcohol exposure and their caregivers. However, child problem behaviors are the primary reason families raising children with FASD seek clinical diagnosis and professional supports (Jirikowic et al., 2010), so this sample is likely to represent those who seek treatment and for whom treatment must be provided. Although caregivers of different types were represented in the study, which is common among this clinical population, a high proportion of caregivers in this study were adoptive parents. This limits the generalization of findings, particularly in regard to birth parents raising children with FASD. Further research is needed to understand the correlates of parenting stress among biological parents and whether types of stress differ by family structure, and these efforts are underway (Salmon, 2008).

Measurement limitations of the SSP are also noted, because 17% of participants in the study were 11 years of age, just outside the range of norms for the SSP (3 to 10 years). However, a post-hoc analysis did not find a significant relationship between age and SSP scores. Finally, the primary outcomes used in this regression analysis were based on parent questionnaires. Future research should validate parent report measures using performance-based child assessments, such as direct testing of executive function (e.g., classic executive function measures, ecologically valid assessments of executive dysfunction, and multi-tasking), and physiological reactivity to sensation. These methods may shed additional light on the strong interrelationships found between caregiver perceptions of sensory processing behaviors, the executive function of behavior regulation, and child problem behaviors.

Conclusion

Both the occupational therapy practice framework and standards for best practices for children with disabilities speak to the need for family-centered approaches and interventions that view the child within the context of the family and environment (American Occupational Therapy Association, 2008; Guralnick, 2001). Knowing the pivotal factors that place the parent–child system at risk in a specific clinical population can guide development of targeted family-centered interventions that support the co-occupation of parenting. For children with FASD, treatment approaches that educate parents about both their children's sensory needs and type of executive function impairment and use strategies for accommodating or remediating these impairments may be promising ways to empower parents with information and tools to help them solve day-to-day parenting challenges. Interventions that help parents raising children with FASD feel more efficacious, improve their cognitive appraisal of their children, and support positive parenting behaviors are being examined (Bertrand & Interventions for Children with Fetal Alcohol Spectrum Disorders Research Consotium, 2009; Olson et al., 2009) and warrant attention as a means to buffer child-related parenting stress and enhance child and family resiliency.

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SENSORY CONTROL OF BALANCE: A COMPARISON OF CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS TO CHILDREN WITH TYPICAL DEVELOPMENT

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ABSTRACT

Background
Inefficient central processing and integration of visual, vestibular, and somatosensory information may contribute to poor balance and diminished postural control in children with fetal alcohol spectrum disorders (FASD).

Objectives
This pilot study examined sensorimotor performance and the sensory control of balance using a battery of clinical tests in combination with an experimental laboratory assessment that quantifies sensory subsystem use (i.e., sensory weighting) among a systematically diagnosed sample of children with FASD and children with typical development.

Methods
Using a case-control design, 10 children with FASD (8.0-15.9 years; 20% female) were compared to 10 age- and sex-matched controls on standardized clinical measures and on kinematic outcomes from the Multimodal Balance Entrainment Response system (MuMBER), a computerized laboratory assessment whereby visual, vestibular, and somatosensory input is manipulated at different frequencies during standing balance.

Results
Children with FASD showed poorer sensorimotor performance across clinical outcomes with significant group differences ($p < .05$) on parent-reported movement behaviors (Sensory Processing Measure and Movement Assessment Battery for Children-2 Checklist) and performance on the Dynamic Gait Index. Experimental kinematic outcomes yielded statistically significant group differences ($p < .10$) on a small proportion of somatosensory and vestibular sensory weighting fractions and postural sway velocity in response to the manipulation of sensory input.

Conclusions
Preliminary findings showed small group differences in sensorimotor and sensory weighting behaviors, specifically those that rely on the integration of vestibular sensation. Differences must be examined and replicated with a larger sample of children with FASD to understand the impact on balance control and functional sensorimotor behaviors.

Key Words: *Fetal alcohol spectrum disorder, prenatal alcohol exposure, postural control, balance, sensory weighting*

Alcohol is a well-established neurobehavioral teratogen. Prenatal alcohol exposure (PAE) can increase the risk for lifelong neurobehavioral problems, as well as developmental and

intellectual disabilities that fall under the umbrella term of fetal alcohol spectrum disorders (FASD). Balance deficits are a more frequent and persistent sensorimotor impairment reported among individuals with FASD.[1-5] Studies examining brain structures in association with PAE have identified cerebellar differences and deficits in cerebellar-dependent behaviors (e.g., gait, balance, and coordination) in both animal models[6,7] and in children.[8,9] Impairments on standardized clinical tests of balance and motor function have also been described among clinically affected children[1,2] and adults.[5] The nature of these balance deficits are not yet fully understood, and clinical assessment and intervention guidance remain limited.

Efficient balance and postural control provide the stability needed to support participation in many higher-level physical, play, and learning activities that promote function and healthy child development.[10,11] Children with impaired or inefficient balance and postural stability may have difficulty with simple tasks that rely on good postural control, such as sitting in a desk, maintaining attention, and learning and controlling complex movements. Poor balance and postural control may also underlie undesirable behaviors that may be misinterpreted as aggression or inattention and contribute to frustration, anxiety, and decreased self-esteem.[12,13,14] Accurately identifying and developing interventions for balance and postural control impairments has the potential to improve postural stability and adaptive motor function as a foundation for participation in childhood activities (e.g., playground activities, organized sports) that promote health and well-being (e.g., social interaction, self-esteem) among this high-risk and underserved clinical population.[15]

Postural control is a complex and dynamic perceptual-motor process that involves the integration of three sensory subsystems (visual, vestibular, and somatosensory), which cue the neuromuscular system to activate postural muscles in response to specific task or environmental conditions.[10,16] The inefficient use of, or adaptation to, sensory information has been explored as a potential mechanism for balance impairments in children with PAE; however, there has been limited replication or expansion of previous findings.[3,4] Roebuck et al[3] used computer posturography to evaluate postural sway while sensory information was manipulated both in accuracy and complexity during standing balance.

The children with PAE had significantly lower composite scores ($p < 0.01$) on the Sensory Organization Test than controls. Results indicated that the children with PAE had adequate postural stability when environmental conditions were stable (i.e., accurate visual and vestibular information), but had more postural sway when somatosensory information was inaccurate (i.e., they were less able to compensate with visual and vestibular information).

Roebuck et al[4] also examined whether the balance deficits among children with PAE were central or peripheral in nature. Twelve children with PAE were compared to 12 controls on postural and neuromuscular responses to movement perturbations using electromyographic (EMG) activity of the lower limbs. No significant group differences were found on short-latency and medium-latency EMG responses, suggesting intact peripheral responsiveness. However, the children with PAE demonstrated more delayed and variable long-latency responses, suggesting poor central processing of sensorimotor information during balance.

Taken together, these study results suggest that inefficient central processing and integration of visual, vestibular, and somatosensory information may play a role in balance and postural control impairments in children affected by PAE. While important, these findings do not precisely specify a child's ability to continually integrate the three sensory subsystems during balance, which is needed to adapt to changing environmental situations. For example, when standing on a moving surface (e.g., boat, escalator, bus) both the feet and the eyes may not give accurate orientation information, therefore, one needs to weight vestibular input to adequately maintain stability.

Recently, an experimental technique has been developed to examine how sensory subsystems integrate to permit successful stabilization for postural control.[16] This technique involves the manipulation of small, barely

perceptible oscillating sensory stimuli (visual field movement or tactile movement) provided at low frequencies in a standing position. The frequency and amplitude of an individual's body sway relative to a particular sensory stimulus frequency and amplitude are examined to determine how a person differentially weights each sensory subsystem for balance control (i.e., sensory weighting).[17,18]

Developmentally, children as young as 4 years have been shown to weight visual and tactile stimuli and shift their response between the two sensory stimuli when stimulus amplitude becomes too large.[19] This capacity to prioritize the reliance on a particular sensory input enhances postural stability in response to changing environmental conditions. In contrast, the inability to weight certain sensory inputs to activate the most efficient and effective postural motor adjustments has been implicated in individuals with postural control impairments and motor deficits.[20]

Sensory weighting between visual and tactile subsystems as a potential mechanism for balance and postural control impairments has not been examined in children with FASD. In addition, manipulations to discover vestibular weighting capabilities in both children with FASD and children with typical development (TD) have not been studied. A clearer understanding of balance impairments among children with FASD is needed in order to develop and evaluate the effects of sensory directed rehabilitation programs, especially in light of the potential for therapeutic motor training to ameliorate motor deficits described in alcohol-exposed animal models.[6,7]

This study had two primary objectives. The first objective was to describe clinical sensorimotor profiles, with an emphasis on the sensory control of balance, of a systematically diagnosed clinical sample of children with FASD compared to an age- and sex-matched control group of children with TD. The second objective was to examine visual, vestibular, and somatosensory weighting during standing balance between the two groups with an experimental laboratory test using kinematic outcome measures. We hypothesized that the children with FASD would show poorer performance on clinical sensorimotor outcomes compared to controls. On kinematic outcomes, we expected that compared to controls, children with FASD would demonstrate poorer postural control (higher velocity and greater area of postural body sway) and would show different sensory weighting fractions as compared to controls when the frequency of sensory input increased.

MATERIALS AND METHODS

This study was approved by the University of Washington Human Subjects Division Institutional Review Board. A sample of children with FASD was recruited from the University of Washington Fetal Alcohol Syndrome Diagnostic and Prevention Network (FAS DPN) clinical registry and database of over 2,500 patients. Participants in the database represent a clinical population of individuals with confirmed prenatal alcohol exposure systematically diagnosed by an interdisciplinary team[21] using the FASD 4-Digit Diagnostic Code.[22,23] The 4-Digit Diagnostic Code is a rigorously defined and extensively validated diagnostic system.[22,24,25] The four digits of the code reflect the magnitude of expression of the key diagnostic features of FASD: (a) growth deficiency, (b) facial features, (c) central nervous system (CNS) structural and/or functional abnormalities, and (d) maternal alcohol consumption during pregnancy. The magnitude of expression of each feature is ranked independently on a 4-point Likert scale with 1 reflecting complete absence of the FAS feature and 4 reflecting a strong "classic" presence of the FAS feature. Each 4-Digit Diagnostic Code falls into unique clinical diagnostic categories, including the following that fall broadly under the designation of FASD: (a) fetal alcohol syndrome/alcohol-exposed (FAS/AE), (b) partial FAS/alcohol-exposed (PFAS/AE), (c) static encephalopathy/alcohol-exposed (SE/AE), and (d) neurobehavioral disorder/alcohol-exposed (ND/AE). See Astley[23] for a full explanation of the 4-Digit Diagnostic Code, diagnostic methods, and categories, and Astley[26] for a profile of the FAS DPN clinical population.

Participants

Ten children with FASD and 10 age- and sex-matched children with typical development (TD) participated in the study. Children in both groups were included in the study if they were ages 8-16 years, male or female, and of any race/ethnicity. Specific inclusion criteria for children with FASD were: confirmed prenatal alcohol exposure at any level, a diagnosis on the fetal alcohol spectrum of FAS, PFAS, SE/AE, or ND/AE, and a previously identified sensorimotor impairment based on clinical diagnostic assessment results. Exclusion criteria for the children with FASD included an IQ < 60 to assure children could adequately follow test directions. In addition, children with severe neuromotor conditions (e.g., cerebral palsy) that impaired ambulation or independent standing for less than 2 minutes, a history of serious head injury, seizures, a visual acuity impairment not corrected by glasses, or a lower limb or back injury within the previous six months were also excluded to control for severe neurological, visual, and orthopedic conditions. Children were recruited and enrolled in accordance with IRB guidelines established for the University of Washington FAS DPN.

Children with TD were recruited from a university research participant pool whose caregivers consented at the time of the child's birth to be contacted for university research studies, through flyers posted in the university community, and by word-of-mouth. Each child with TD was matched to a child in the FASD group by age (± 6 months) and sex. Children with TD were not eligible if, by parent report, they had a sensory or motor impairment, were enrolled in special education or occupational or physical therapy programs, reported any neurological illness/injury, seizure, genetic, metabolic, behavioral, cognitive disorders, or had a lower limb or back injury within the previous six months. Children in the comparison group were excluded from the study if during the enrollment screen caregivers reported prenatal alcohol exposure of ≥ 3 drinks (defined as ½ oz absolute alcohol = 12 oz beer = 5 oz wine= 1 oz of 100 proof spirit) prior to pregnancy recognition or during the pregnancy.

Procedures

Children were tested during a 2.5-hour laboratory visit. Assessments were administered in the same order by an occupational therapist or physical therapist trained in the assessment battery and who was masked to group status. Each parent completed three questionnaires.

Instrumentation

Measures to describe the participants were:

1. *Demographic Questionnaire:* Parent questionnaire to gather demographic, child health, and developmental information.
2. *Anthropometric Measures:* Child's height, weight, and foot size.
3. *Clinical Sensory Screen:*[27] Child's responses to light touch and light pressure on each foot and lower leg. A limb position test and limb movement test examined proprioception and kinesthesia. Responses were scored as pass or fail.
4. *Clinical Strength, Range of Motion, and Posture Screen:* Child's lower extremity range of motion and strength were examined, and standing posture for scoliosis, kyphosis, lordosis, leg length difference, and standing foot position were observed.
5. *Kaufman Brief Intelligence Test-2, Matrices Subtest (K-BIT-2):*[28] A measure of non-verbal intelligence for persons 4-90 years to estimate cognitive level. For children 4-18 years, good internal reliability (α = .86 - .92), test-retest reliability (r = .83 - 91), and construct validity have been reported. The Matrices Subtest standard score was the variable of interest with higher scores indicating better performance.

Standardized clinical measures of sensorimotor behaviors and adaptation during static and dynamic balance activities were:

1. *Movement Assessment Battery for Children-2nd edition (MABC-2):*[29] A measure of motor skills in children 3-16 years. Internal reliability (α = 0.90) and test-retest reliability for the total score are high (ICC = 0.97).[30] The Balance subtest scaled score is reported with higher scores indicating better performance.

2. *Sensory Processing Measure (SPM):*[31] A standardized parent questionnaire for children 5-12 years that examines child behavioral responses to touch, movement, visual, and auditory input. Internal reliability (α = .77-.95), inter-rater reliability (r > .94), and construct validity have been reported. Balance subsection and total score T scores are reported, with higher scores indicating more behaviors indicative of poor sensory processing.
3. *Pediatric Clinical Test of Sensory Interaction for Balance-2 (P-CTSIB-2):*[32] Static balance was assessed under six systematically altered sensory conditions. The conditions were: (1) eyes open standing on floor, (2) eyes closed standing on floor, (3) sway-referenced vision via wearing a dome with eyes open standing on floor, and (4-6) the three visual conditions repeated while standing on medium-density memory foam. Total ordinal score and vestibular (condition 5 + 6) sensory system scores are reported; higher scores indicate better performance. Test-retest reliability (ICC[2,1]=.67-.89), inter-rater reliability (ICC[2,1]=.49-.92), and validity are adequate.[33,34]
4. *Movement Assessment Battery for Children-2nd edition Checklist (MABC-2 Checklist):*[29] Parent questionnaire that examines child movement behaviors in everyday situations, including movement in static or predictable environments and in dynamic or unpredictable environments. Raw scores for each subtest are reported with lower scores indicating better performance.
5. *Dynamic Gait Index (DGI):*[35] Eight walking tasks test dynamic balance during vestibular challenges (e.g., walking 20' while turning head right and left, stepping over obstacles). Adequate test-retest reliability (ICC[2,1] = .71) and construct validity have been demonstrated in children.[36] The total raw score is reported with higher scores indicating better performance.

Laboratory measure of sensory weighting:

MultiModal Balance Entrainment Response (MuMBER) system: This computerized laboratory assessment system was developed based, in part, on the work of Jeka et al.[18] This experimental method measures sensory weighting across sensory subsystems by determining the fraction between body sway frequency and sensory stimulus frequency during standing balance under varying sensory conditions. The construct validity of the MuMBER system as sensitive measure of sensory system weighting has been demonstrated, as children with and without FASD showed changes in sensory weighting behaviors as sensory input was introduced and as sensory stimuli frequency was increased. Within session trial-to-trial reliability of sensory weighting is fair.

During the MuMBER protocol, participants stood on a piece of medium-density memory foam (5 cm thick) overlaid on a platform that tilts (vestibular stimulus), faced a visual screen that displayed a field of horizontally moving dots (visual stimulus), and rested the right index finger on a moveable touch pole (somatosensory stimulus) (Figure 1). The finger pressure on the touch pole was regulated to light touch indicated by a tone. If the child pressed too hard (>5N), the tone would stop and the examiner would assist the child to the correct touch pressure. A helmet (weighing 1.5 kg) restricted peripheral vision to the screen (approximately 110° horizontally and 45°vertically) and white noise was played through earphones during the trials to mask touch pole and platform noise. A safety harness was attached to an overhead trolley to prevent falls. Participants were instructed to stand with feet together, keep their finger resting on the touch pole, look at the screen, and then do whatever felt natural.

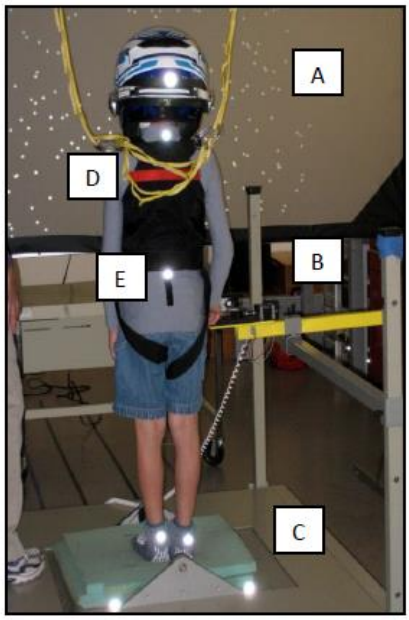


FIG. 1 MultiModal Balance Entrainment Response (MuMBER) system components:

A. Moveable visual screen dots (visual stimulus), **B**. touch pole for right index finger (somatosensory stimulus), **C**. moveable platform surface with foam overlay (vestibular stimulus). **D**. Safety harness for fall protection. **E**. Reflective markers for motion capture on heels, sacrum, spine, and head (helmet).

Sensory stimuli were provided in various combinations of Low (L), Medium (M), and High (H) frequencies for visual (dots on screen), somatosensory (touch pole), and vestibular (platform support surface) inputs, under fixed amplitudes (Table 1). For example, as the frequencies increased the dots, touch pole, and platform oscillated medially-laterally at a faster rate. Stimulus conditions were grouped in a sequence where the frequency of one sensory system increased from L, to M, to H while the other two were held at low frequency stimulation. Each stimulus was triggered to move in a medial-lateral direction at a specific frequency unique to each sensory stimulus and at consistent small amplitudes. Two trials of 60 seconds duration each, over seven test conditions, were applied (Table 1). A Qualysis Oqus 300 motion analysis system[37] captured body sway movements at 120 Hz through five cameras located posterior and lateral to the child. The system tracked five reflective markers located on the head (helmet), seventh cervical (C7) vertebra, sacrum between the posterior superior iliac crests, and Achilles tendons, approximately 5 cm above the inferior surface of each heel. Postural sway was tracked in response to the changing sensory stimulation, and kinematic data were used to determine the proportion that the child weighted each stimulus as the frequency of sensory movement was altered. The expectation was that children would decrease sensory weighting to high frequency stimuli due to the potential destabilizing effect on their balance.

TABLE 1 Multi Modal Balance Entrainment and Response (MuMBER) Protocol: Visual, Somatosensory and Vestibular Conditions

Condition[1, 2]	Acronym[3]	Visual Freq. [Hz] (V)	Somatosensory Freq. [Hz] (T)	Vestibular Freq. [Hz] (P)
All systems low	LLL	0.32	0.24	0.40
Medium V, low T, low P	MLL	0.57	0.24	0.40
High V, low T, low P	HLL	1.01	0.24	0.40
Low V, medium T, low P	LML	0.32	0.59	0.40
Low V, high T, low P	LHL	0.32	1.11	0.40
Low V, low T, medium P	LLM	0.32	0.24	0.52
Low V, low T, high P	LLH	0.32	0.24	0.86

[1]Amplitude range was kept constant as follows: visual dots (visual stimulus) = 9 mm medial-lateral; touch-pole (somatosensory stimulus) = 4 mm medial-lateral; platform tilt (vestibular stimulus) = 0.25º tilt; [2]V = Visual; T = Somatosensory; P = Vestibular; [3]L = low frequency movement; M = medium frequency movement; H = high frequency movement

Data Reduction

All kinematic data were examined frame by frame for missing data. If markers momentarily disappeared due to the child's body movements (e.g., if the child extended his head, the helmet could obscure the C7 marker; if the child's safety vest shifted it could obscure the C7 or sacral marker), those segments were interpolated. Any trials with a marker gap (>300 ms) were discarded. Each marker component was centered, by subtracting the mean, before further processing. Spectral analysis was conducted using custom LabVIEW software to derive the magnitude of the sacrum marker movement at the three sensory stimuli movement frequencies for the seven conditions tested. To derive the sensory weighting variables, we calculated the fraction, defined as the magnitude of (medial-lateral) body sway at each sensory frequency divided by all other peaks of body sway movement at other frequencies (Figure 2).

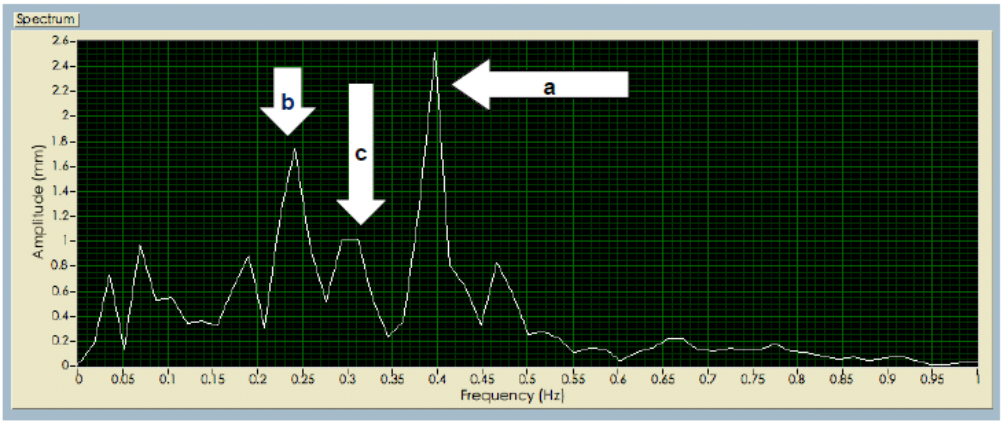


FIG. 2

Spectral analysis from the sacrum marker of one participant derived from Labview software for an LLL condition. a) Peak at the vestibular frequency 0.4Hz; b) Peak at the somatosensory frequency 0.24Hz; c) Peak at the visual frequency 0.32Hz.

The vestibular weighting fraction, somatosensory weighting fraction and visual weighting fraction are calculated as a/N, b/N and c/N, respectively, where N is the sum of all peaks observed. The methodology relies on stimulating the various balance subsystems, each with its own unique stimulus frequency, to reveal how much each subsystem contributes to the whole. The total response (i.e., marker motion) is broken down into frequency and amplitude components (i.e., spectral analysis), and the results across stimulus frequencies are compared. For each stimuli response the amplitude vs. frequency data form distinct amplitude peaks at specific frequencies (i.e., response peaks), which often, but not exclusively, correspond to the stimulus frequencies. For example, a response peak at the frequency of the somatosensory stimulus would suggest a large somatosensory subsystem contribution (weighting). The fraction of the somatosensory response peak to the total of all response peaks provides a relative weighting metric for the somatosensory subsystem. Two kinematic postural control variables were derived by sensory condition using MatLab software: (1) velocity of body sway movement (root mean square mm/sec), and (2) area of the ellipse of body sway (cm^2). The mean of two trials per sensory condition was used for all analyses. Outcomes from all body markers yielded similar trends, however, because the sacral marker is closer to the body center of mass and had fewer missing data points (as compared to the C7 marker where the helmet obscured more data points) only data from the sacral marker are reported for all analyses.[38]

Data Analysis

Descriptive statistics were used to summarize demographic, standardized sensorimotor clinical outcomes and sensory weighting/postural sway kinematic outcomes. Due to the small sample size, we used a non-parametric Wilcoxon signed-rank test for paired data to compare the performance of children with FASD to children with TD. Two-tailed significance levels were set at $\alpha = 0.05$ for clinical outcomes and $\alpha = 0.10$ for experimental outcomes (MuMBER). Since this is the first study to use MuMBER outcome variables, the study has an exploratory and preliminary nature, and corrections for multiple comparisons were not applied.

RESULTS

Sample Demographics

Personal characteristics for both groups are presented in Table 2. Matching during sampling produced comparable age and sex distributions. Only one child with FASD was in the care of a biological parent, whereas all 10 children with TD had a biological parent listed as primary caregiver. Groups were similar on parent level of education; however, all families of the TD group had income greater than $75K, compared to three families of the group with FASD. The mean intellectual estimate was lower for the children with FASD than children with TD. We refrained from doing hypothesis testing for group differences since the sample size was small, and due to self-selection (especially of the control group), the groups are not likely to be representative of the entire population of caregivers.

Clinical sensory, strength, range of motion, and posture screen measures were grossly intact and comparable between groups with one exception. A higher proportion of children with FASD (50%) than children with TD (10%) were unable to complete trunk force flexion testing for 30 seconds. A similar proportion of children in each group demonstrated minor postural or musculoskeletal differences that included postural lordosis (FASD 40%; TD 60%), hyper-pronated feet (FASD 50%; TD 40%), and borderline to mild signs of scoliosis (FASD 30%; TD 20%).

Standardized Clinical Measures of Sensorimotor Behaviors and Balance

Mean and median scores on child performance and caregiver-reported sensorimotor outcomes are reported by group in Table 3. The median scores for children with FASD suggested clinically poorer performance than the children with TD across all clinical sensorimotor measures. Statistically significant differences ($p < 0.05$) were seen on the MABC-2 checklist and SPM, indicating more parent-reported balance problems during functional movement for the children with FASD. The children with FASD also had significantly lower median scores on the DGI;

lower scores on the MABC-2 Balance and P-CTSIB-2 total ordinal and vestibular scores approached significance.

TABLE 2 Personal and Demographic Characteristics by Group

Characteristic	FASD (n= 10)	TD (n = 10)
Age in months		
Mean (SD)	142.2 (30.4)	144.5 (30.2)
Median (Min, Max)	130.5 (111, 186)	133.0 (113, 187)
Sex, % of females	20.0	20.0
Caregiver relationship to child, %		
Biological parent	10.0	100.0
Adoptive/legal guardian/other	90.0	0.0
Caregiver level of Education,%		
High School Diploma	10.0	0.0
Some College	20.0	10.0
College or Professional Degree	70.0	90.0
Annual income		
< $25,000	10.0	0.0
$25,000 to $50,000	20.0	0.0
$50,000 to $75,000	40.0	0.0
> $75,000	30.0	100.0
K-BIT-2 Matrices[1]		
Mean (SD)	90.8 (19.2)	112.7 (12.4)
Median (min, max)	97 (56, 100)	116.5 (93,129)
FASD diagnosis, %		
FAS/pFAS[2]	20.0	0.0
Static encephalopathy/alcohol exposed	50.0	0.0
Neurobehavioral disorder/alcohol exposed	30.0	0.0

[1] Kaufman Brief Intelligence Test-2, Matrices Subtest (K-BIT-2).
[2] Fetal Alcohol Syndrome (FAS)/partial fetal alcohol syndrome

Laboratory (kinematic) Measures

Table 4 and Figure 3 show the visual, somatosensory, and vestibular fractions across sensory conditions manipulated at low, medium, and high frequencies and group comparisons. Overall, both children with and without FASD systematically decreased sensory weighting as the stimulus frequency increased. *Visual median weighting fractions* were not statistically different between groups across the seven conditions tested. *Somatosensory median weighting fractions* were significantly different for two of the conditions tested: LLL ($p = 0.09$), with the children with FASD showing a lower median weighting fraction, and HLL ($p = 0.07$), with the children with FASD showing a slightly higher median weighting fraction. A statistically significant difference in one *Vestibular median weighting fraction* for the LLL condition ($p = 0.09$) was found. Clinical significance cannot yet

be determined as this is a new measure utilized only in the sample tested for this study. Postural control outcomes (median body sway area and velocity) were almost uniformly higher for the group of children with FASD; with a statistically significant group difference in sway velocity in the LLH condition (p = .07) (Table 5) suggesting poorer postural control in the children with FASD compared to children with TD.

TABLE 3 Standardized clinical measures of sensorimotor behaviors and adaptation during static and dynamic balance by group

Measures of Sensorimotor Behaviors and Balance	FASD	TD	p value[5]
MABC Balance Total[1]			
Mean (SD)	8.5 (2.7)	11.3 (3.1)	
Median (min, max)	9.0 (5.0, 14.0)	12.0 (6.0, 14.0)	.08
MABC Checklist A Static (raw score)			
Mean (SD)	7.1 (4.8)	.8 (1.9)	
Median (min, max)	7.0 (1.0, 15.0)	0.0 (0.0, 6.0)	.02
MABC Checklist B Dynamic (raw score)			
Mean (SD)	10.5 (7.2)	.4 (1.0)	
Median (min, max)	10.5 (0.0, 24.0)	0.0 (0.0, 3.0)	.01
SPM Total Score[2]			
Mean (SD)	63.7 (6.6)	46.8 (8.2)	
Median (min, max)	65.0 (47, 69)	43.0 (40, 60)	.007
SPM Balance [2]			
Mean (SD)	58.0 (10.7)	49.4 (9.6)	
Median (min, max)	59.5 (40, 71)	47.0 (40, 61)	.04
DGI Total Score[3]			
Mean (SD)	21.4 (1.4)	23.2 (1.1)	
Median (min, max)	21.0 (19, 24)	24.0 (21, 24)	.02
P-CTSIB-2 Static Ordinal Total[4]			
Mean (SD)	27.6 (2.3)	29.1 (1.1)	
Median (min, max)	28.5 (22,30)	29.5 (27, 30)	.07
P-CTSIB-2 Vestibular			
Mean (SD)	8.2 (1.4)	9.3 (1.1)	
Median (min, max)	8.5 (5, 10)	10.0 (7, 10)	.06

[1]Movement Assessment Battery for Children 2nd edition (MABC-2; standard score M = 10, SD=3); [2]Sensory Processing Measure (SPM; T score; M = 50, SD=10). [3]Dynamic Gait Index (DGI; raw score) – missing 1 pair; [4]Pediatric Clinic Test of Sensory Interaction for Balance-2 (P-CTSIB-2; raw score). [5]Wilcoxon signed-rank test for paired data.

TABLE 4 Sensory weighting fractions: Sensory condition by group

Sensory Condition[1,2]	Visual Fraction		Somatosensory Fraction		Vestibular Fraction	
	TD	FASD	TD	FASD	TD	FASD
LLL						
Mean (SD)	.11 (.03)	.11 (.03)	.12 (.03)	.10 (.02)	.13 (.04)	.16 (.06)
Median	.11	.12	.12	.11	.13	.15
(Min, Max)	(.07, .15)	(.06, .17)	(.07, .18)	(.06, .13)	(.06, .23)	(.10, .29)
p value[3]	0.51		0.09		0.09	
MLL						
Mean (SD)	.05 (.01)	.05 (.01)	.12 (.02)	.11 (.03)	.14 (.05)	.19 (.05)
Median	.05	.05	.12	.11	.14	.19
(Min, Max)	(.04, .06)	(.02, .07)	(.08, .15)	(.06, .14)	(.05, .22)	(.11, .26)
p value[3]	0.57		0.45		0.20	
HLL						
Mean (SD)	.02 (.005)	.02 (.02)	.12 (.03)	.10 (.02)	.17 (.06)	.15 (.02)
Median	.02	.02	.12	.09	.16	.15
(Min, Max)	(.01, .03)	(.01, .08)	(.07, .16)	(.08, .12)	(.06, .29)	(.12, .20)
p value[3]	0.72		0.07		0.45	
LML						
Mean (SD)	.12 (.04)	.11 (.03)	.05 (.02)	.05 (.02)	.15 (.04)	.17 (.06)
Median	.11	.12	.04	.04	.16	.15
(Min, Max)	(.08, .20)	(.07, .15)	(.03, .08)	(.03, .08)	(.06, .20)	(.12, .27)
p value[3]	0.88		0.65		0.39	
LHL						
Mean (SD)	.12 (.02)	.12 (.03)	.01 (.003)	.02 (.006)	.15 (.04)	.18 (.06)
Median	.11	.12	.01	.01	.15	.17
(Min, Max)	(.08, .15)	(.08, .17)	(.01, .02)	(.01, .03)	(.08, .21)	(.11, .29)
p value[3]	0.58		0.39		0.14	
LLM						
Mean (SD)	.12 (.03)	.11 (.04)	.13 (.03)	.11 (.04)	.10 (.04)	.10 (.04)
Median	.11	.11	.13	.12	.09	.09
(Min, Max)	(.06, .18)	(.06, .17)	(.07, .16)	(.05, .16)	(.02, .15)	(.06, .17)
p value[3]	0.45		0.33		0.96	
LLH						
Mean (SD)	.15 (.03)	.12 (.05)	.13 (.03)	.14 (.05)	.04 (.01)	.05 (.01)
Median	.15	.11	.13	.13	.04	.05
(Min, Max)	(.09, .20)	(.09, .23)	(.08, .19)	(.09, .23)	(.02, .05)	(.03, .07)
p value[3]	0.20		0.65		0.20	

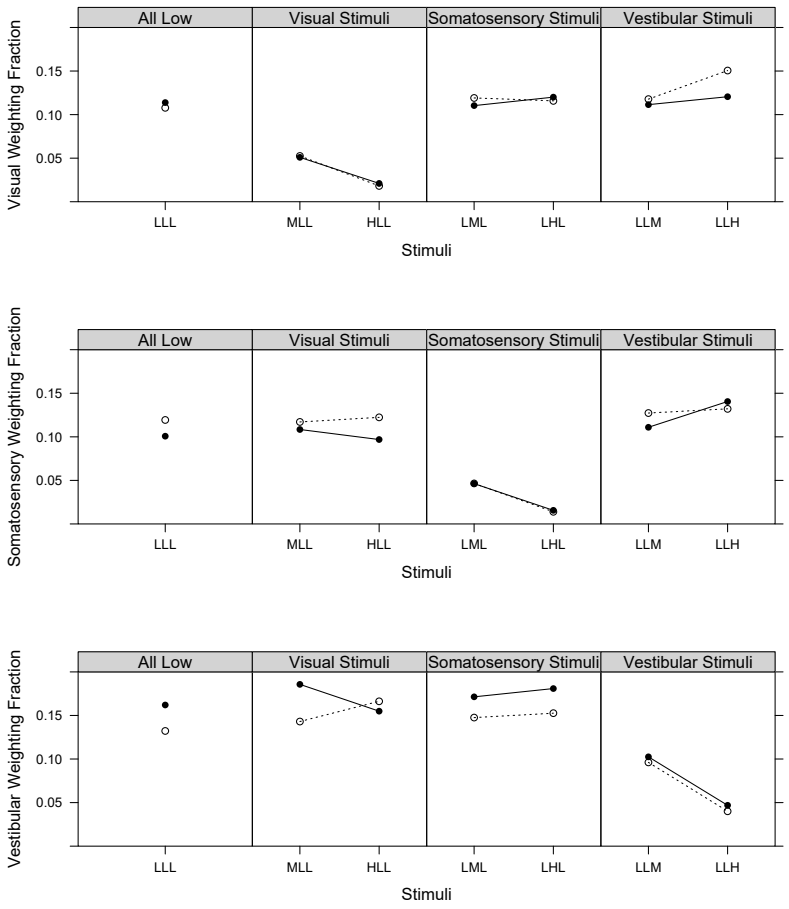
[1]Sensory conditions are presented in the following order visual, somatosensory, vestibular (e.g., **MLL** = visual stimulus at **M**edium frequency; somatosensory stimulus at **L**ow frequency; vestibular stimulus at **L**ow frequency).
[2] L = low frequency movement; M = medium frequency movement; H = high frequency movement. [3]Wilcoxon signed-rank tests for paired data.

TABLE 5 Postural control measures by group

Sensory Condition[1,2]	Ellipse of body sway area (mm^2) Sacrum		Velocity (RMS)[3] Sacrum	
	TD	FASD	TD	FASD
LLL				
Mean (SD)	15.5 (6.5)	14.2 (6.7)	10.4 (1.5)	10.9 (1.5)
Median	14.1	12.9	10.3	10.3
(min, max)	(5.2, 24.3)	(6.8, 26.2)	(7.9, 12.4)	(9.6, 14.2)
p value[4]	0.44		0.59	
MLL				
Mean (SD)	14.7 (6.3)	19.9 (14.1)	10.8 (1.5)	13.0 (4.4)
Median	12.7	16.1	11.0	12.1
(min, max)	(8.7, 28.2)	(8.0, 54.3)	(8.5, 13.4)	(9.8, 24.2)
p value[4]	0.52		0.26	
HLL				
Mean (SD)	15.3 (6.2)	16.6 (7.9)	10.4 (1.6)	12.8 (2.3)
Median	13.3	15.6	10.4	12.0
(min, max)	(8.4, 25.5)	(6.7, 32.4)	(8.0, 13.6)	(10.2, 17.6)
p value[4]	0.95		0.11	
LML				
Mean (SD)	14.4 (6.8)	14.0 (6.0)	10.8 (1.4)	11.4 (1.5)
Median	13.3	14.3	11.4	11.5
(min, max)	(5.6, 26.4)	(5.2, 25.2)	(8.6, 13.0)	(9.0, 14.0)
p value[4]	0.95		0.59	
LHL				
Mean (SD)	17.0 (8.1)	16.7 (7.5)	10.5 (2.0)	11.8 (1.2)
Median	15.5	17.2	10.2	11.7
(min, max)	(7.2, 31.8)	(6.3, 26.2)	(7.4, 14.1)	(9.9, 13.8)
p value[4]	0.77		0.26	
LLM				
Mean (SD)	16.5 (11.6)	15.7 (9.2)	10.4 (1.8)	12.0 (2.8)
Median	11.9	12.7	10.2	11.5
(min, max)	(8.0, 45.0)	(9.3, 38.8)	(7.8, 13.1)	(9.2, 19.0)
p value[4]	0.95		0.37	
LLH				
Mean (SD)	15.2 (5.2)	16.8 (12.8)	10.8 (1.8)	14.0 (5.8)
Median	16.3	14.8	10.9	12.3
(min, max)	(6.5, 22.0)	(6.0, 48.2)	(7.6, 13.2)	(10.3, 29.0)
p value[4]	0.37		0.07	

[1]Sensory conditions are presented in the following order visual, somatosensory, vestibular (e.g., **MLL** = visual stimulus at **M**edium frequency; somatosensory stimulus at **L**ow frequency; vestibular stimulus at **L**ow frequency).
[2]L = low frequency movement; M = medium frequency movement; H = high frequency movement; [3]RMS = root mean square; [4]Wilcoxon signed-rank tests for paired data.

FIG. 3 Visual, somatosensory, and vestibular weighting fractions across conditions: Children with FASD are depicted in solid circles and children with TD are depicted in open circles.



DISCUSSION

This pilot study is the first to describe the sensory control of balance using an experimental assessment system that quantifies the sensory weighting of visual, somatosensory, and vestibular stimuli in combination with clinical sensorimotor tests among a systematically diagnosed sample of children with FASD and children with TD. Our overall results describe and replicate evidence of diminished functional sensorimotor performance on clinical measures for children with FASD compared to matched controls with TD. Our experimental outcome of sensory weighting yielded a small proportion of statistically significant group differences on somatosensory and vestibular sensory weighting fractions and postural sway velocity. Significant group contrasts were not found on other clinical and kinematic (postural control) measures that focused on the sensory control of balance. We interpret findings from our experimental measure

as evidence of possible differences in how efficiently children with FASD adapt to and use sensory subsystems, namely vestibular input, for balance control. These findings are small and preliminary given our limited sample size, and the clinical significance of our experimental sensory weighting outcomes needs further validation.

Clinical Measures

As expected, given the range of alcohol-related diagnoses of the children with FASD in this sample, standardized clinical measures yielded a heterogeneous descriptive profile of sensorimotor performance. As a group, the children with FASD generally had intact strength, musculoskeletal integrity, and peripheral responses to sensation. Mean and median scores on standardized clinical sensorimotor measures suggested poorer balance and functional sensorimotor performance for the children with FASD than their counterparts with TD. The children with FASD scored approximately 1 standard deviation lower than controls on the MABC-2 Balance subtest. Caregivers of the children with FASD almost uniformly reported difficulties with day-to-day movement behaviors on the SPM and MABC-2 checklist. This demonstrates the difficulties children with FASD have using motor and postural skills efficiently in the context of complex, dynamic tasks and environments.[2] While the results of the caregiver-reported measures (SPM and MABC-2 checklist) for participants older than age 12 (30%) should be interpreted with caution, as they were beyond the upper age limits of the normative sample, the latter findings are consistent with previous research.[2]

Mixed results were seen on clinical measures that examined the sensory control of balance under static and dynamic conditions. We found statistically significant group differences on the DGI, which measures gait quality during dynamic vestibular conditions. The lower score for the children with FASD on this measure suggests that the children with FASD demonstrated less efficient vestibular processing in response to dynamic vestibular challenges. However, the clinical significance of these subtle differences requires more investigation as the DGI has not been utilized extensively with children.

Group differences on the P-CTSIB-2, a clinical measure of the sensory control of balance, approached statistical significance for the total score and vestibular score. We consider the lower mean scores for the children with FASD as clinically significant and suggestive of decreased postural stability under complex sensory conditions (i.e., inaccurate or conflicting sensory information). We base this on previous testing of children with balance disorders with the P-CTSIB and P-CTSIB-2 in which most children ages 4-9 years receive the maximum total score.[39,40] Therefore, any deviation from a maximum total point score suggests a clinically significant difference, especially since the mean age of the children with FASD in our sample was 11.9 years. Poorer performance on the P-CTSIB-2 is aligned with previous research findings in children with PAE of similar age who showed less efficient vestibular processing during standing balance under altered sensory conditions.[3]

Sensory Weighting Measures

Using our novel laboratory MuMBER measurements, we have described and quantified how children in both groups weight visual, vestibular, and somatosensory information with the aim of examining how children differentially utilize each subsystem to control overall stability. Children in both groups showed similar decreases in sensory weighting for all subsystems as the frequency of the sensory stimuli increased. This suggests that all of the children could unweight from potentially destabilizing visual, somatosensory, and vestibular sensory stimuli. However, two interesting group differences in the sensory weighting outcomes were seen. First, the children with FASD showed consistently higher vestibular sensory weighting fractions than controls across most conditions. Second, the children with FASD showed consistently higher velocity of body sway (observed as "jerky" movements) to control standing balance as compared to controls across all of the sensory conditions.

These findings suggest that the children with FASD had less efficient postural stability specifically in response to the platform stimuli (±0.25 degree of medial-lateral tilt). We

hypothesize that the children with FASD were less able to actively synchronize their body sway to the subtle platform support surface movement. This, in turn, may have caused their body movement to be "dragged" by the platform movement, resulting in higher vestibular sensory weighting fractions in comparison to the children with TD. Children with TD appeared to react to the tilting by coordinating their movements opposite to the platform movement, resulting in smaller sway amplitudes and fractions. This hypothesis will need to be tested further with larger samples of children with FASD.

Taken together, our clinical and experimental findings are consistent with, and expand, previous research that suggests that children affected by PAE demonstrate poorer postural stability and static balance[2] and have more difficulty adapting when sensory (i.e., vestibular) information is inaccurate.[3] However, this study was preliminary and had a small sample size, and therefore, any statistically significant group differences need to be corroborated in larger studies powered to confirm findings. Results from our laboratory measurement system need replication in larger samples of children with and without FASD. Further, we observed that younger children (8-9 years) with and without FASD demonstrated poorer postural control during the computerized laboratory assessment compared to older controls. This agrees with other findings that suggest that sensory integration for postural control does not fully mature until adolescence.[41] We did not test enough children in either group to estimate the effect of developmental differences, but this warrants further study.

The overall severity of postural disability in the children with FASD was minimal to moderate, despite our effort to include children with FASD who had a history of sensorimotor dysfunction. In further exploration of the data utilizing only the seven matched pairs with children with FASD who had more "severe" diagnosis on the fetal alcohol spectrum (i.e., FAS or SE/AE) there were statistically significant differences between the groups on all clinical measures, but differences on the MuMBER sensory weighting fractions were unchanged. Examining larger samples of children with more moderate to severe postural control impairments is needed to better understand the clinical utility of the MuMBER system.

Despite study limitations, our results are congruent with other descriptive studies that report a range of sensorimotor abilities (from subtle to clinically significant impairments) in individuals clinically affected by PAE.[2,5] Our focus on the measurement of sensory weighting behaviors provides new and more precise information about how children with and without FASD integrate sensory information to control balance. Our comprehensive sensorimotor profile that included both clinical and kinematic outcomes was an attempt to more precisely test whether the inefficient central processing of sensation, in particular vestibular input, plays a role in diminished postural control and functional sensorimotor performance among children with FASD. Further investigation is warranted to more fully understand how children with FASD use and integrate visual, vestibular, and somatosensory information during balance under both experimental and naturalistic conditions and how this capacity affects functional movement behaviors.

Acknowledgements

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VALIDATION OF THE FETAL ALCOHOL SPECTRUM DISORDER (FASD) 4-DIGIT DIAGNOSTIC CODE

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ABSTRACT

Background
The fetal alcohol spectrum disorder (FASD) 4-Digit Diagnostic Code has been used by interdisciplinary diagnostic teams worldwide for 17 years. It was created to improve the ease, accuracy, and reproducibility of diagnoses across the full spectrum of FASD. Over the years, a number of FAS/D diagnostic guidelines have been proposed. As the field of FASD moves forward, it will be important to adopt a single set of diagnostic guidelines worldwide. To achieve this, the performance (validity) of current diagnostic guidelines must be rigorously assessed and reported.

Objective
To summarize the body of evidence that has amassed over 20 years that validates the performance of the FASD 4-Digit Diagnostic Code.

Methods
The evidence validating the 4-Digit Code is documented across 35 studies published between 1992 and 2012, including new information presented in this report. These studies and data sources include the delineation of the FAS facial phenotype; creation of the 4-Digit Code (1997-2004); our 10-year, foster-care FAS screening program; our MRI/fMRI/MRS studies; analysis of 2,550 individuals evaluated for FASD over 20 years in the WA State FASDPN clinics, and analysis of 622 patient satisfaction/follow-up surveys; surveys of 10,000 professionals attending the University of Washington FASD diagnostic clinic trainings; and surveys of over 700 professionals worldwide who completed the 4-Digit Code Online Course.

Conclusion
The 4-Digit Code is a simple, comprehensive, evidence-based, validated diagnostic system. It has served as the cornerstone of a fully integrated FASD screening, diagnostic, intervention, prevention, and surveillance program in Washington State for the past 20 years.

Key Words: *Fetal alcohol spectrum disorders (FASD), fetal alcohol syndrome (FAS), diagnosis, validity, 4-Digit Diagnostic Code, FAS Diagnostic & Prevention Network (FASDPN)*

The fetal alcohol spectrum disorder (FASD) 4-Digit Diagnostic Code has been used by interdisciplinary diagnostic teams worldwide for 17 years (Figure 1).[1-3] It was created to improve the ease, accuracy, and reproducibility of diagnoses across the full spectrum of FASD.[4] Over the years, a number of FAS/D diagnostic guidelines have been proposed.[5-8] As the field of FASD moves forward, it will be important to adopt a single set of diagnostic guidelines worldwide.[9] To achieve this, the performance (validity) of current diagnostic guidelines must be empirically assessed and reported. The purpose of this report is to pull together the body of evidence that has amassed over 20 years that validates the performance of the FASD 4-Digit Diagnostic Code. This report highlights key evidence, directing readers to the source publications for more details.

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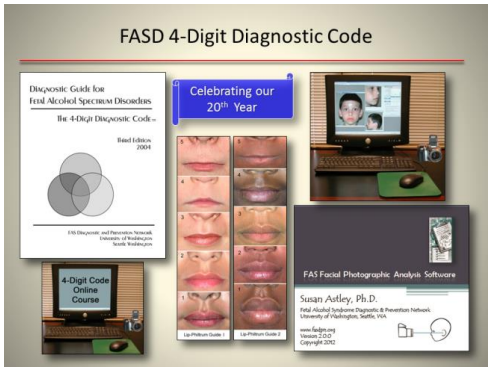
FIG. 1 A. The FASD 4-Digit Diagnostic Code is supported by a number of tools including the Guidelines, Lip-Philtrum Guides, FAS Facial Photographic Analysis Software, and Online Course. All are distributed free or at cost on the FASDPN website. B. Interdisciplinary diagnostic team.



A

B

What is FASD?

Fetal alcohol syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. The definition of FAS has changed little since the 1970's when the condition was first described and refined.[5,10-13] The condition has been broadly characterized by prenatal and/or postnatal growth deficiency, a unique cluster of minor facial anomalies, and central nervous system (CNS) abnormalities. FAS is the leading known and preventable cause of intellectual disabilities in the Western World.[14] The prevalence of FAS is estimated to be 1 to 3 per 1,000 live births[5] in the general U.S. population, but has been documented to be as high as 10 to 15 per 1,000 in some higher-risk populations such as children residing in foster care.[15]

The physical, cognitive, and behavioral deficits observed among individuals with prenatal alcohol exposure are not dichotomous, that is either normal or clearly abnormal. Rather, the outcomes, and the prenatal alcohol exposure, all range along separate continua from normal to clearly abnormal and distinctive.[16-19] This full range of outcomes observed among individuals with prenatal alcohol exposure has come to be called Fetal Alcohol Spectrum Disorders (FASD). Diagnoses like FAS, Partial FAS (PFAS), Static Encephalopathy / Alcohol Exposed (SE/AE), and Neurobehavioral Disorder / Alcohol Exposed (ND/AE) fall under the umbrella of FASD[4].

The Diagnostic Challenge

FASD can present a daunting, but not insurmountable challenge for diagnosis. Individuals with prenatal alcohol exposure present with a wide range of outcomes, most of which are not specific to prenatal alcohol exposure and often manifest differently across the lifespan. Professionals from multiple disciplines (medicine, psychology, speech-language pathology,

occupational therapy, etc.) are needed to assess and interpret accurately the broad array of outcomes that define the diagnoses.[20] The pattern and severity of outcomes are dependent on the timing, frequency, and quantity of alcohol exposure (which is rarely known with any level of accuracy), and is frequently confounded by other adverse prenatal and postnatal exposures, events, and conditions.

In the absence of objective, accurate, and reproducible methods for measuring and recording the severity of exposures and outcomes in individual patients, diagnoses use to vary widely from clinic to clinic.[4,5,21-23] From a clinical perspective, diagnostic misclassification leads to inappropriate patient care, increased risk for secondary disabilities, and missed opportunities for primary prevention.[4] From a public health perspective, diagnostic misclassification leads to inaccurate estimates of incidence and prevalence.[4,5,8,23] Inaccurate estimates thwart efforts to allocate sufficient social, educational, and health care services to this high-risk population, and preclude accurate assessment of primary prevention intervention efforts.[4,15,24] From a clinical research perspective, diagnostic misclassification reduces the power to identify clinically meaningful contrasts between FAS and control groups and between FASD clinical subgroups like FAS and ARND.[4,16,25,26] Non-standardized diagnostic methods also thwart valid efforts to compare outcomes between research studies.[16,17,27]

FASD Diagnostic Guidelines

FASD diagnostic guidelines have evolved over time since the term FAS was first coined in the medical literature in 1973.[9] Early guidelines were gestalt (purposely broad and conceptual) in nature and administered primarily by geneticists and dysmorphologists.[4,9] The Institute of Medicine (IOM) FASD guidelines[5] published in 1996 would be the last in this line of gestalt approaches to diagnosis. In 1997, the FASD 4-Digit Diagnostic Code was introduced to overcome the limitations of the gestalt approach to diagnosis.[1] It proposed an interdisciplinary approach to diagnosis guided by rigorously and empirically case-defined criteria.[20] In 2004-2005, three additional FAS/D diagnostic guidelines were published: the CDC FAS guidelines[6] in July 2004; the Revised IOM FASD guidelines[8] in January 2005, and the Canadian FASD guidelines[7] in March 2005. The 4-Digit Code was subsequently updated in January, 1999[2] and November 2004.[3] Why are there four separate guidelines? Their existence reflects the ongoing debate on how best to approach FASD diagnosis. All present with strengths and limitations.[9] Each was developed under different circumstances that influenced their outcome. The 4-Digit Code was investigator initiated in a statewide clinical/research arena using a large clinical sample of 1,014 individuals of all races and ages (birth to 51 years of age).[4] Empirical methods were used both to develop[28-30] and validate the performance of the 4-Digit Code.[4,9,15-17,23-26] The CDC[6] and Canadian[7] guidelines were federally mandated and commanded a more consensus-driven process. These guidelines were not empirically validated prior to publication. The Revised IOM[8] guidelines were also investigator initiated in a clinical/research arena, using a clinical sample of 164 Native American and South African children to augment an existing set of gestalt guidelines: the 1996 IOM Guidelines. All four of these guidelines have been compared/contrasted in detail by Astley in 2010.[9] In Astley's summary remarks, she reports "*The field should strive to adopt a single set of diagnostic guidelines for FASD*". This same conclusion was drawn at a recent meeting of FASD diagnostic guideline authors at the March 2013 International FASD conference in Vancouver British Columbia. It is important to note that the process of selection has long been underway by clinicians worldwide. It is clinicians who will ultimately decide which diagnostic guidelines best meet their needs and the needs of their patients and families. To guide this selection process, it will be essential for the authors of the various guidelines to validate (assess the performance) of their guidelines. Validity must be confirmed, not assumed, through properly designed empirical studies.[5]

Assessing a Diagnostic Tool's Performance (Validity)

Validity is the degree to which a tool (or diagnostic system) is measuring what it purports to measure.[31] Validity is not determined by a single statistic, but by a body of research that demonstrates the relationship between the diagnostic system and the condition it is intended to measure. There are three overarching forms of validity: **content validity, criterion validity, and construct validity**. **Content Validity** is a measure of how well the items in the diagnostic system represent the entire range of possible items the diagnostic system should cover. **Criterion validity** is a measure of a diagnostic tool's accuracy relative to a gold standard. **Construct validity** refers to the degree to which a test measures what it claims, or purports, to be measuring. It refers to the ability of a measurement tool to measure the physiological concept being assessed. Convergent and discriminant validity are two subtypes of construct validity. **Convergent validity** refers to the degree to which two measures of constructs that theoretically should be related are in fact related. In contrast, **discriminant validity** tests whether concepts or measurements that are supposed to be unrelated are in fact unrelated. An important aspect of clinical research is the inference that an association represents a cause-effect relationship. Features of associations that support causation include: the strength of the association; the consistency of observed evidence; specificity of the relationship; temporality of the relationship; the biological gradient of dose-response, biological plausibility; and experimental confirmation. **Predictive validity** refers to a tool's ability to predict something is should theoretically be able to predict. **Precision (Accuracy)** is the degree to which a measurement procedure produces the correct answer. **Reliability (Reproducibility)** is the degree to which a measurement procedure produces the same result each time. **Test-Retest Reliability** is the variation in measurements taken by a single person on the same item and under the same conditions**. Inter-rater Reliability** is used to assess the consistency of a test across two or more raters. **Intra-rater Reliability** is the degree of agreement among multiple repetitions of a diagnostic test performed by a single rater. Statistical measures used to assess these constructs include linear correlation coefficients, tests for trends, and Kappa statistics. Fundamental measures of diagnostic accuracy include sensitivity and specificity. The **sensitivity** of a test is the proportion of people with the condition who test positive for it (the true positive rate). The **specificity** of a test is the proportion of people who do not have the condition who test negative for it (the true-negative rate). **Positive Predictive Value (PPV)** is the probability that a patient with a positive test result really does have the condition. **Negative Predictive Value (NPV)** is the probability that a patient with a negative test result really does not have the condition. The body of research presented below that validates the performance of the FASD 4-Digit Code utilized all of these measures.

Introduction to the FASD 4-Digit Code

The FASD 4-Digit Code is described in full by Astley.[3] Briefly, the 4 digits of the FASD 4-Digit Code reflect the magnitude of expression of the 4 key diagnostic features of FASD, in the following order: 1) growth deficiency, 2) FAS facial phenotype, 3) CNS structural/functional abnormalities, and 4) prenatal alcohol exposure (Figure 2A). The magnitude of expression of each feature is ranked independently on a 4-point Likert scale, with 1 reflecting complete absence of the FASD feature and 4 reflecting a strong "classic" presence of the FASD feature. Each Likert rank is specifically case defined. There are a total of 102 4-Digit Codes that fall broadly under the umbrella of FASD (Table 2). These codes cluster under four clinically meaningful FASD diagnostic subcategories: fetal alcohol syndrome (FAS): Diagnostic Categories A and B; Partial FAS (PFAS): Diagnostic Category C; Static Encephalopathy/Alcohol-Exposed (SE/AE): Diagnostic Categories E and F; and Neurobehavioral Disorder/Alcohol-Exposed (ND/AE): Diagnostic Categories G and H (Figure 2B). The attributes of the 4-Digit Code are summarized in Table 3

A Validation Guide

As clinicians assess the performance of FAS/D Diagnostic Guidelines, they may find the list of questions presented in Table 1 a helpful guide.

TABLE 1: As clinicians assess the performance of FASD diagnostic guidelines, clinicians should ask the following questions. The answer to all of these questions is 'yes' for the FASD 4-Digit Diagnostic Code.

1. Have properly designed studies been published to confirm the case definition for the FAS facial phenotype is highly specific (>95%) to FAS and alcohol (e.g. observed only among individuals with prenatal alcohol exposure and FAS)?
2. Was data used to empirically derive the diagnostic guidelines? Was the data drawn from a large, representative, population-base?
3. Has the performance of the guidelines been empirically assessed (validated)?
4. Individuals are born with FAS/D. Can the diagnostic system identify FAS/D at birth and across the lifespan?
5. Growth deficiency, the FAS facial phenotype, CNS abnormalities, and alcohol exposure all present along clinically meaningful continuums. The FAS facial phenotype is not just present or absent. The brain is not just normal or abnormal. Do the Guidelines recognize/incorporate these important continuums?
6. Do the guidelines produce clinically distinct subgroups across the full spectrum (FAS, PFAS, SE/AE, ND/AE)?
   A. Do brain imaging studies identify statistically significant contrasts between the FASD subgroups?
   B. Individuals with FAS have more severe CNS dysfunction than individuals with "ARND". Do the Guidelines generate FAS and "ARND" groups that demonstrate this important contrast?
   C. Do individuals who meet the criteria for FAS actually have FAS?
7. Can the guidelines detect unique alcohol exposure patterns between the FASD subgroups?
8. Can the diagnostic system be effectively and efficiently taught to interdisciplinary teams?
9. Are the guidelines confirmed to be reproducible? If two clinics use the guidelines, do they render the same diagnoses?
10. Do families report high satisfaction/confidence with the diagnostic process/outcome?
11. Are the names of the diagnoses (FAS, PFAS, SE/AE, ND/AE) medically valid? Do they imply causality between alcohol and outcome that cannot be confirmed in the individual patient?
12. Do diagnoses under the umbrella of FASD qualify patients for intervention services that lead to improved outcomes?

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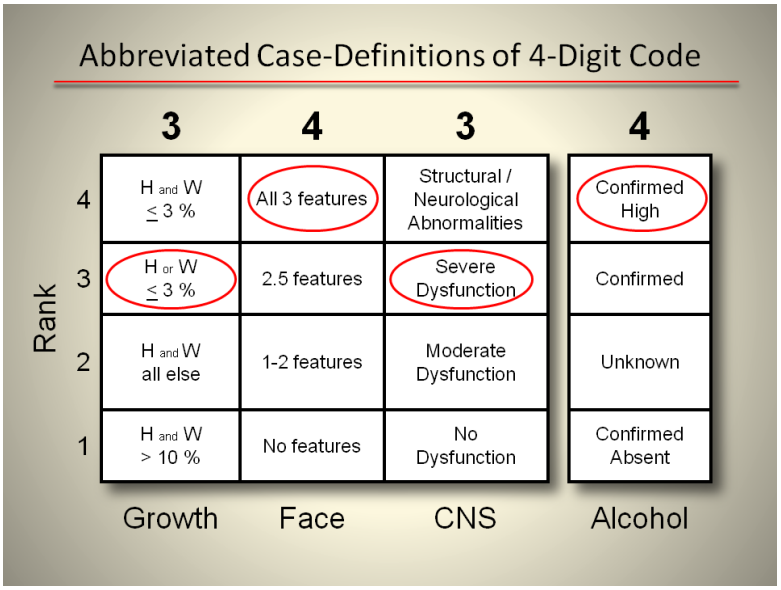
FIG. 2 A. Abbreviated case-definitions of the FASD 4-Digit Code.[3] The 4-Digit Code 3434 is one of 12 Codes that fall under the diagnostic category FAS (Table 2). B. The 4-Digit Code produces four diagnostic subgroups under the umbrella of FASD: FAS, PFAS, SE/AE, and ND/AE.[16,26] The 4-Digit Code uses the terms SE/AE and ND/AE in place of the term ARND.



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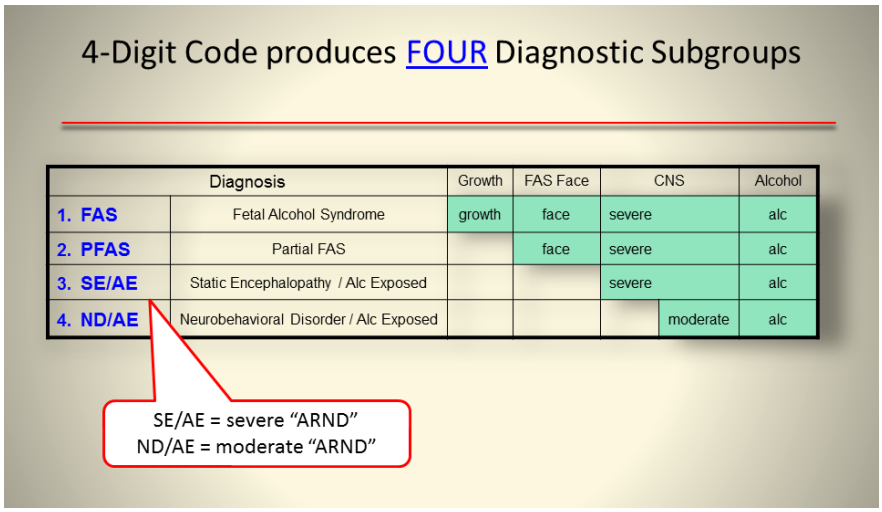

B

Validation of the fetal alcohol spectrum disorder (FASD) 4-Digit Diagnostic Code

TABLE 2 4-Digit Diagnostic Codes within each FASD Diagnostic Category (2004)[3]

A. FAS / Alcohol Exposed

2433	3433	4433	
2434	3434	4434	
2443	3443	4443	
2444	3444	4444	

B. FAS / Alcohol Exposure Unknown

2432	3432	4432	
2442	3442	4442	

C. Partial FAS /Alcohol Exposed

1333	1433	2333	3333
1334	1434	2334	3334
1343	1443	2343	3343
1344	1444	2344	3344

E. Sentinel Physical Finding(s) / Static Encephalopathy / Alcohol Exposed

3133	3233	4133	4233
3134	3234	4134	4234
3143	3243	4143	4243
3144	3244	4144	4244

F. Static Encephalopathy / Alcohol Exposed

1133	1233	2133	2233
1134	1234	2134	2234
1143	1243	2143	2243
1144	1244	2144	2244

G. Sentinel Physical Finding(s) / Neurobehavioral Disorder / Alcohol Exposed

1323	2323	3123	3323	4123	4323
1324	2324	3124	3324	4124	4324
1423	2423	3223	3423	4223	4423
1424	2424	3224	3424	4224	4424

H. Neurobehavioral Disorder / Alcohol Exposed

1123	1223	2123	2223
1124	1224	2124	2224

TABLE 3 Key Attributes of the FASD 4-Digit Diagnostic Code.[4]

1. Greatly increases diagnostic precision and accuracy through the development of objective, quantitative measurement scales (e.g., Lip-Philtrum Guides), facial analysis software, and specific, operational case definitions.
2. Diagnoses the full spectrum of outcomes across the lifespan.
3. Was developed empirically using a large, representative, population-base.
4. Offers an intuitively logical numeric approach to reporting outcomes and exposure that reflects the true diversity and continuum of disability observed in individuals with prenatal alcohol exposure.
5. Uses the universal language of numbers, thus facilitating ease of reporting worldwide. The numeric base also allows rapid and easy update of large datasets as diagnostic criteria are refined.
6. Establishes a method for case-defining the highly variable, nonspecific CNS dysfunction that typifies FASD, by quantifying the breadth and magnitude of dysfunction (number of domains of function 2 or more SDs below the mean) without unduly constraining which domains must be impaired.
7. Establishes diagnostic subclassifications that capture the full spectrum of FASD without inferring alcohol is the sole causal agent.
8. Documents all other prenatal and postnatal adverse exposures and events that can also impact outcome.
9. Provides a quantitative measurement and reporting system (the 4-Digit Code) that can be used independent of the diagnostic nomenclature.
10. Has received extensive assessment/validation of its performance.
11. Was designed for use by an interdisciplinary FASD diagnostic team.
12. Is readily taught to interdisciplinary teams through an Online Course, thus greatly expanding the availability of diagnostic services worldwide.
13. Qualifies patients for intervention services that produce improved outcomes.
14. Receives high satisfaction/confidence ratings from families and clinicians

Data sources used to assess/validate the FASD 4-Digit Diagnostic Code

The 4-Digit Code is a simple, comprehensive, evidence-based, validated diagnostic system (Figure 1).[9] The performance of the 4-Digit Code was assessed (validated) prior to its initial release in 1997 and extensively thereafter. The evidence supporting the validation of the 4-Digit Code is documented across over 35 studies published between 1992 and 2012, including new information presented in this report. These studies include the empirical delineation of the FAS facial phenotype (1992-2001)[25,28-30,32]; the creation and updates of the 4-Digit Code (1997-2004)[1-3]; a 10-year population-based FAS active screening/surveillance study of foster care using 2D facial photographs and the FAS Facial Photographic Analysis Software (1999-2009)[15,24,33]; WA State Pregnancy Risk Assessment Monitory System (PRAMS) public health surveillance data documenting annual maternal use of alcohol during pregnancy (1993-99)[34]; the MRI/fMRI/MRS studies (2002-2007)[16,17,27,35]; analysis of over 2,000 fields of data

on over 2,550 alcohol-exposed individuals evaluated for FASD over the course of 20 years in the seven WA State FASDPN clinics (1993-2013)[26], analysis of 577 patient satisfaction/follow-up surveys over 20 years[26]; surveys of over 10,000 professionals attending the UW FASD diagnostic clinic trainings (1993-2013); and surveys of over 700 professionals worldwide who completed the 4-Digit Code Online Course (2004-2013).

A synopsis of the published evidence validating the performance of the 4-Digit Code is presented in Table 4. Each entry in Table 4 is described in full in the body of this report, identified numerically to match the entry in Table 4.

TABLE 4 Synopsis of published evidence validating the performance of the FASD 4-Digit Code. Each entry in this Table is described in full in the body of this report.

1. The 4-Digit Code was created in 1997 to overcome the limitations of the gestalt approach to FASD diagnosis used from 1973-1996. Its advanced performance was empirically confirmed prior to its publication. The 4-Digit Code:
    - A. Produced more accurate, homogeneous diagnostic subgroups.
    - B. Detected clinically important correlations between growth, face, brain, and alcohol that the gestalt method failed to detect.
    - C. Demonstrated high inter- and intra-rater reliability.
    - D. Had a FAS facial phenotype with confirmed high sensitivity and specificity to FAS and prenatal alcohol exposure.
2. The Quintessential Role of the FAS Facial Phenotype
    - A. The full FAS Facial Phenotype (Rank 4):
        1. Is confirmed to be highly sensitive and specific (>95%) to FAS and alcohol and does not vary by race, gender or age.
        2. Serves as the most efficient/effective way to screen for FAS in population-based samples
        3. Is uniquely correlated with significantly and disproportionately smaller frontal lobe volumes which is consistent with midventral forebrain deficiencies associated with facial dysmorphia observed in animal studies of alcohol teratogenicity.
        4. Is quintessential to the validity of all diagnoses under the umbrella of FASD, not just FAS.
    - B. The FAS Facial Phenotype presents on a Continuum:
        1. Presents on a continuum that is significantly correlated with (predictive of) abnormal brain structure and function.
        2. Can be measured easily and accurately from a 2D photo using the FAS Facial Photographic Analysis Software.
3. The 4-Digit Code's method for case-defining the highly variable CNS dysfunction that typifies FASD demonstrates high construct validity.
    - A. The 4-Digit Code's method for classifying CNS dysfunction (CNS Ranks 1, 2, and 3) successfully predicts underlying CNS structural abnormality, as it was designed to do. For example, the more severe the CNS dysfunction (CNS Ranks 1,2 and 3), the smaller the caudate volume.
    - B. Microcephaly predicts severe CNS dysfunction among infants/toddlers who present with the full Rank 4 FAS facial phenotype.
4. The 4-Digit Code generates four distinct diagnostic subgroups (FAS, PFAS, SE/AE, and ND/AE), under the umbrella of FASD.

Validation of the fetal alcohol spectrum disorder (FASD) 4-Digit Diagnostic Code

A. The 4 diagnoses are clinically and statistically distinct and span the full continuum of FASD.
    1. Individuals with FAS have growth deficiency, those with PFAS do not.
    2. Only FAS/PFAS have the FAS face, small frontal lobe volumes, and reduced choline levels.
    3. Only FAS/PFAS and SE/AE have small caudate volumes.
    4. FAS/PFAS have more severe CNS dysfunction than SE/AE.
    5. SE/AE have more severe CNS structural/functional abnormalities than ND/AE.
    6. ND/AE have CNS structural abnormalities underlying their moderate CNS dysfunction.
    7. Even families detect/report clear distinctions between the diagnostic subgroups.
B. Extensive evidence validates the inclusion of individuals with moderate dysfunction (ND/AE) under the umbrella of FASD.
C. The term ARND (like Fetal Alcohol Effects) should be abandoned and replaced with medically valid terms like SE/AE and ND/AE that do not imply causation.

5. The 4-Digit Code's method of documenting prenatal alcohol exposure not only detects significant correlations between exposure and outcomes, but also detects exposure patterns that distinguish the diagnostic subgroups.
    A. The 1-page standardized form used to record prenatal alcohol exposure patterns effectively addresses the challenges of documenting exposure. Full information is rarely available. Despite this, the 4-Digit Code method can:
        1. Detect significant correlations between alcohol exposure and measures of growth, face, and CNS abnormalities.
        2. Identify exposure patterns among FAS/PFAS that are distinct from SE/AE and ND/AE.
    B. The prevalence of maternal alcohol use during pregnancy correlates with the prevalence of FAS as defined by the 4-Digit Code.
    C. An 'excessive' alcohol exposure history should not be required for a diagnosis under the umbrella of FASD for the following reasons:
        1. As tools become more sensitive, our ability to detect adverse outcomes improves.
        2. Risk varies among individuals, even between twins.
        3. Sends the wrong public health message "moderate exposure is safe?"
        4. Reliable histories on quantity/frequency/timing of exposure are rarely available.
        5. Only allowing high exposures to be associated with adverse outcomes prevents identifying the true dose-response relationship between alcohol and adverse outcomes.
6. The 4-Digit Code has been effectively and efficiently taught to interdisciplinary FASD diagnostic teams worldwide through an inexpensive Online Course.
7. The 4-Digit Code is reproducible across clinics. Of 677 patients diagnosed across 7 WA FASD Clinics, >93% received a diagnosis that matched the diagnosis rendered by the core clinic at the University of Washington.
8. Families report high satisfaction and confidence with the interdisciplinary approach to FASD diagnosis using the 4-Digit Code.
9. Patient follow-up surveys confirm all FASD diagnoses (FAS, PFAS, SE/AE, and ND/AE) provided equal access to intervention services that led to improved outcomes.

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1 The 4-Digit Code was created in 1997 to overcome the limitations of the gestalt approach to FASD diagnosis. Its advanced performance relative to the gestalt approach was empirically confirmed prior to its publication.

When the University of Washington CDC-sponsored FASD diagnostic clinic first opened in January 1993, it was the first to propose/implement an interdisciplinary approach to diagnosis.[20,36-38] The interdisciplinary team (medical doctor, psychologist, speech language pathologist, occupational therapist, social worker, and family advocate) used the most current FASD diagnostic guidelines available at that time; the 1989 gestalt diagnostic criteria published by Sokol and Clarren.[13] In 1996, the IOM published an updated set of FASD diagnostic guidelines[5], but continued to propose a gestalt approach. The gestalt approach to diagnosis presented with many limitations as outlined in Astley & Clarren.[1,4] The 4-Digit Code was created in 1997 to overcome these limitations.[1] The medical/research records of the first 1,014 patients diagnosed at the Washington State FAS Diagnostic and Prevention Network of clinics were used to develop the 4-Digit Diagnostic Code.[4] Importantly, this was a representative statewide population of patients spanning all ages and races. To assess the performance of the 4-Digit Code, the subset of 454 patients who had received a gestalt diagnosis under the umbrella of FASD (FAS, atypical FAS, or possible fetal alcohol effect (PFAE)) were retroactively coded on the 4-Digit Code to empirically compare the FASD classification outcomes of the two diagnostic systems.[4] The superior performance of the 4-Digit Code relative to the gestalt approach to diagnosis is briefly summarized below.

1A The 4-Digit Code produced homogeneous FASD diagnostic subgroups. The gestalt method of diagnosis produced highly variable FASD diagnostic subgroups.

For example, of the first 454 patients who received a gestalt diagnosis under the umbrella of FASD, 69 were classified as FAS. In the absence of rigorous guidelines, this group was very heterogeneous.[4] Of the 69 subjects with a gestalt diagnosis of FAS: only 32 had growth deficiency ($\leq$10th percentile); only 27 had the Rank 4 FAS face; and only 40 had significant CNS structural/functional abnormalities. When the more rigorous 4-Digit Code was applied to the 69 with a gestalt diagnosis of FAS only 9 of the 69 retained a diagnosis of FAS. Twelve were reclassified to Partial FAS; 18 were reclassified to Static Encephalopathy /Alcohol Exposed (SE/AE); 26 were reclassified to Neurobehavioral Disorder / Alcohol Exposed (ND/AE); and 4 were not even on the spectrum (exposure unknown).

1B The 4-Digit Code detected clinically important correlations between growth, face, brain, and alcohol that the gestalt method failed to detect.

Inter-correlations between growth, face, brain, and alcohol, confirmed to exist in laboratory-based studies of alcohol teratogenicity[29,39], were completely absent in our clinical population when the gestalt method was used, and strongly significant when the 4-Digit Code was used. For example, the hypothesis that the full-scale intelligence quotient (FSIQ) decreases with increasing magnitude of expression of the FAS facial phenotype was tested among 216 patients who had been diagnosed by both the gestalt and 4-Digit diagnostic systems.[4] Of the 216 patients, 31 were identified as having the gestalt FAS facial phenotype. The difference in the mean FSIQ between the patients with and without the gestalt FAS facial phenotype (82.3 and 85.0 respectively) was not statistically significant ($t = -1.56$, $p = 0.13$). In contrast, when the same 216 patients were classified by their 4-point Likert rank reflecting the magnitude of expression of the 4-Digit Code FAS facial phenotype, the difference in the mean FSIQ between the patients with and without the full FAS facial phenotype (78.5 and 87.7 respectively) was statistically significant ($t = 2.3$, $p = 0.02$). More importantly, a statistically significant, inverse, linear association was revealed. The mean FSIQs among the patients

with FAS Facial Ranks of 4 (severe), 3 (moderate), 2 (mild), and 1 (absent) were 78.5, 83.8, 84.8 and 87.7 respectively (f = 4.1, p = 0.04). Thus, a clinically important linear association between face and brain that was detected by the 4- Digit Code, failed to be detected by the gestalt method of diagnosis. This illustrates two important points: First, in the absence of specific case definitions, the gestalt approach results in diagnostic misclassification. This explains why the mean FSIQs for the groups with and without the gestalt FAS facial phenotype did not differ significantly. Individuals who truly did not have the FAS facial phenotype were misclassified as having the gestalt FAS face. Their inclusion in the gestalt FAS group erringly elevated the mean FSIQ for that group. Note the mean FSIQ for the gestalt FAS facial group was 82.8 while the mean FSIQ for the 4-Digit Rank 4 FAS facial group was 78.5. Second, the gestalt method of diagnosis records the FAS facial phenotype on a dichotomous scale (present, absent). The 4-Digit Code records the FAS facial phenotype on a 4-point Likert scale (Rank 1. Absent; Rank 2. mildly present; Rank 3. moderately present; Rank 4. severely present). In reality, growth, face, brain and alcohol all present along clinically meaningful continuums. The 4-Digit Code captures all outcomes and exposures on ordinal or continuous scales. Ordinal and continuous scales have far greater statistical power than dichotomous (e.g., present, absent) scales to detect important correlations that will not only advance our understanding of FASD, but provide us with more sensitive diagnostic tools. For example, one challenge in FASD diagnosis is to confirm or rule-out CNS dysfunction in children too young to participate in comprehensive neuropsychological testing. We now know that the subset of young children at greatest risk for CNS dysfunction is the subset who present with a Rank 2, 3 or 4 FAS facial phenotype. The higher the facial rank, the higher the risk.[9,25] The face is such a strong predictor of underlying CNS dysfunction, we recommend these children receive early intervention based on the presence of this physical risk factor. Postponing intervention until CNS dysfunction manifests would deny the child access to the benefits of early intervention. The correlation between the magnitude of expression of the 4-Digit FAS facial phenotype and CNS abnormality is presented more fully in section 2B.

<u>1C</u> The 4-Digit Code had confirmed high inter-rater and intra-rater reliability.

A core goal of the 4-Digit Code was to establish a diagnostic system that was reproducible (reliable) across clinicians and clinics. No matter where a patient was seen, they would receive the same FASD diagnostic outcome. This diagnostic precision and accuracy were achieved through the development of objective, quantitative measurement scales (e.g. Lip-Philtrum Guides) and specific, operational case definitions. The creation of the FAS Facial Photographic Analysis Software[33,40], web-based instructional videos and animations, and the FASD 4-Digit Code Online accredited course[41] further enhanced diagnostic precision and accuracy. This rigorous, case-defined approach is what sets the 4-Digit Code apart from the gestalt approach to diagnosis. The Code's reliability was confirmed to be high prior to its publication.[4] The 4-Digit Codes of 20 randomly selected patient files were re-derived independently by two clinicians, while masked to the original 4-Digit code that had been derived 1-4 years ago by the University of Washington diagnostic team. The re-derived codes matched the original 4-Digit Codes across all four digits for all 20 subjects (inter- and intra-rater reliability was 100%, (Kappa = 1.0, p = 0.000). The 4-Digit Codes for the 20 randomly selected patients spanned the entire spectrum of Neurobehavioral Disorder to Partial FAS (1124 to 1444). Inter-rater reliability between the six FASDPN regional clinics and the University of Washington FASDPN Core clinic resulted in an exact match across all four digits on 15 of 16 (94%) patients (Kappa = 0.93, p = 0.000) and an exact match on Diagnostic Category on all 16 (100%) of the patients (Kappa = 1.0, p = 0.000). The one 4-Digit code that did not match was coded by the regional FASDPN clinic as 1223 and the University FASDPN clinic as 1123. The mismatch in the facial score was due to the network physician not pulling the epicanthal fold back before measuring

the palpebral fissure length resulting in an underestimate of the length. Diagnostic inter-rater reliability between the six FASDPN regional clinics and the University of Washington FASDPN Core clinic continues to be high (93% match in FASD Diagnostic Category across 677 patients over the next 18 years (Kappa = 0.92, p = 0.000)).

1D The Rank 4 FAS facial phenotype was confirmed to have high sensitivity and specificity to FAS and prenatal alcohol exposure.

Prior to the creation of the 4-Digit Code, a decade of research was conducted to empirically identify and case-define the cluster of minor facial anomalies that were most sensitive and specific (>95%) to FAS and prenatal alcohol exposure.[15,25,28-30,32] This is described more fully below.

2 The quintessential role of the FAS facial phenotype.

The FAS facial phenotype is the cornerstone of FASD diagnostic guidelines (Table 5). Two core principles are important to understand: 1) The high sensitivity and specificity of the full FAS facial phenotype is essential to the validity of all diagnoses under the umbrella of FASD, not just the diagnosis labeled FAS. 2) The FAS face is not simply present or absent. It presents on a clinically meaningful continuum that is highly predictive of underlying structural and functional brain abnormalities. Each of these principals is discussed more fully below.

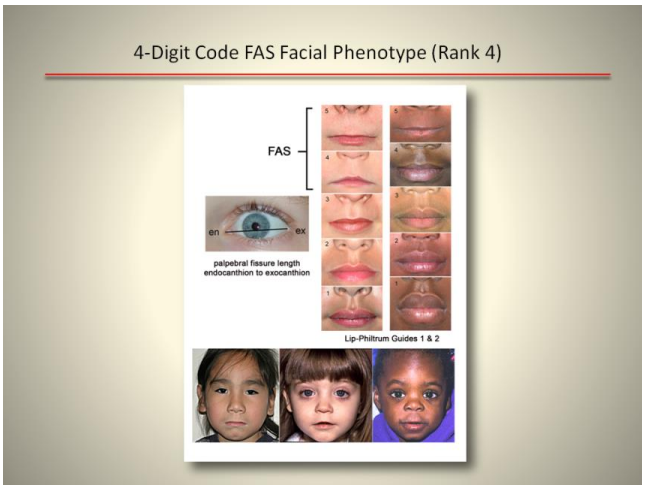
TABLE 5 4-Digit Code FAS facial phenotype fundamentals.

1. Empirically identified and case-defined 18 years ago.
2. Presents along a clinically meaningful continuum (absent, mild, moderate, severe: Facial Ranks 1,2, 3, 4 respectively).
3. This continuum is significantly correlated with (predictive of) brain abnormality. The more severe the face, the more severe the underlying structural and functional brain abnormality.
4. This face can be identified across all ages and races and does not diminish with age.
5. The Rank 4 FAS Face is confirmed to be highly sensitive and specific (>95%) to FAS and prenatal alcohol exposure. This high specificity is the only reason a diagnosis of FAS to be rendered when alcohol exposure is unknown.
6. If the criteria for the FAS facial phenotype are relaxed, sensitivity and specificity are substantially reduced.
7. A diagnosis of (FAS/Alcohol Exposure Unknown) cannot be made if the FAS facial phenotype used to render that diagnosis is not highly specific to prenatal alcohol exposure. Specificity must be empirically confirmed, not assumed.
8. The full continuum of the 4-Digit Code FAS facial phenotype is easily and accurately measured from a 2D digital photo using a $60 piece of software (FAS Facial Photographic Analysis Software). This ease, accuracy, and low cost of measurement is why 2D was selected over 3D.
9. The most accurate and efficient method to screen for full FAS is to identify the Rank 4 facial phenotype from a 2D digital facial photo (as demonstrated by the 10-year foster care FAS screening program in Seattle).

2A The full (Rank 4) FAS facial phenotype.

The full (Rank 4) FAS facial phenotype, as defined by the 4-Digit Code, is the simultaneous expression of the following three minor facial anomalies: 1) short palpebral fissure lengths (PFL) (2 or more SDs below the mean ($\leq$ 2.5th percentile)); 2) Smooth philtrum (Rank 4 or 5 on the Lip-Philtrum Guide); and 3) thin upper lip (Rank 4 or 5 on the Lip-Philtrum Guide) (Figure 3).[4]

FIG. 3 The full (Rank 4) FAS facial phenotype, as defined by the 4-Digit Code, is the simultaneous expression of the following three minor facial anomalies: 1) short palpebral fissure lengths (PFL) (2 or more SDs below the mean); 2) Smooth philtrum (Rank 4 or 5 on the Lip-Philtrum Guide); and 3) thin upper lip (Rank 4 or 5 on the Lip-Philtrum Guide)[3]. The FAS facial phenotype does not vary by race, as demonstrated in photos of three children with the Rank 4 FAS facial phenotype (Native American, Caucasian, and African American).



2A.1 The full FAS facial phenotype (Rank 4) is highly sensitive and specific (>95%) to FAS and prenatal alcohol exposure and does not vary by race, gender or age.

If the Rank 4 FAS facial phenotype is truly unique to prenatal alcohol exposure (e.g., alcohol is the only agent that can cause this facial phenotype) and is unique to the diagnosis of FAS (e.g., this exact phenotype is not present in any other medical condition), then one would expect to observe the following: 1) this facial phenotype would be highly sensitive to FAS (e.g., individuals with FAS would have the FAS facial phenotype), 2) this face would be highly specific to FAS (e.g., individuals without FAS would not have the FAS facial phenotype), and 3) this face would be highly specific to prenatal alcohol exposure (e.g., individuals with confirmed absence of prenatal alcohol exposure would not have the FAS facial phenotype). The Rank 4 FAS facial phenotype, as defined by the 4-Digit Code, demonstrates all three of these qualities. [24,25,28-30]

Empirical studies were conducted over the course of 10 years to identify and case-define the cluster of minor facial anomalies that had the highest sensitivity and specificity to FAS.[15,25,28-30,32,42] The Rank 4 FAS facial phenotype is > 95% sensitive and specific to FAS and prenatal alcohol exposure.[28,30] Sensitivity and specificity were

confirmed to be unaffected by race, gender, and age.[25] The Rank 4 FAS facial phenotype presents across all races, is identifiable at birth, and does not diminish with age.[9] Twenty years of FASD clinic and 10 years of FAS screening in foster care bear this out. This FAS facial phenotype has been accurately measured and diagnostically classified in thousands of individuals across every race (e.g., 1,958 Caucasian, 596 African American, 360 Native American, 254 Hispanic, 48 Asian) and combination of race without limitation This is achieved by using measurement scales normalized to race, gender, and age, as appropriate. And, although it has been a long held belief in this field "*that some FAS craniofacial anomalies may be less evident at birth, become more conspicuous during early infancy and childhood, and often diminish or even disappear during adolescence and adulthood"*[5], our experience over 20 years confirms this does not hold true.[26] This belief stemmed largely from three studies published in the 1980s and 90s that assessed the qualitative change in facial features among children who presented with gestalt features of FAS.[43-45] Back then an ever growing list of minor facial anomalies was being attributed to FAS. Most of the features that were reported to diminish with age (flat nasal bridge, epicanthal folds, short upturned nose, and retrognathia): had never been confirmed to be sensitive or specific to prenatal alcohol exposure; and were remarkably consistent with descriptions of normal facial growth. Enlow and Hans[46] report that when one compares the face of a normal child to that of a normal adult, the child's nose is short and upturned, the nasal bridge is low, often resulting in epicanthal folds, and the mandible is small and retrusively placed. Interestingly, the FAS features reported not to change with age (short PFL, smooth philtrum, and a thin upper lip) are the only features that the 4-Digit Code will subsequently confirm to be sensitive and specific to prenatal alcohol exposure, and match the features originally identified as defining the face of FAS by David Smith, M.D. back in 1979. As stated by Smith.[47] "*As far as the diagnosis is concerned, perhaps the most important point to emerge in the last few years is that the facial abnormalities seen in affected infants are the key cluster of features that tend to make FAS a clinically discernible entity. Many disorders result in mental and growth deficiency, but in FAS the deficiencies are typically present in a patient whose face has short palpebral fissures, a hypoplastic upper lip with a thinned vermilion border and a smoothed or absent philtrum. Up to now, the descriptions of the facial features of FAS that have appeared in the literature have not always emphasized the same abnormalities. This has led to some confusion, but inspection of the photographs accompanying these reports leaves no doubt about the facial similarities of FAS patients*." Further evidence that the FAS facial phenotype (as defined by the 4-Digit Code) does not diminish with age stems from our experience conducting FASD diagnostic evaluations on thousands of individuals over 20 years.[26] Although we typically see individuals just once to render a diagnosis, we have seen over 100 children at two time points, typically as toddlers and again as adolescents. No child had a FAS facial phenotype that diminished with age when measured using reliable measurement techniques (eg. Lip-Philtrum Guides and FAS Facial Photographic Analysis Software[33]). We also routinely request childhood (or younger) facial photos of all patients requesting an FASD diagnostic evaluation. Among the 1,279 patients providing us with younger pictures of themselves, again, we have never seen the FAS facial phenotype (as defined by the 4-Digit Code) diminish with age.

When the diagnostic criteria for the FAS facial phenotype are relaxed, the phenotype is no longer sufficiently sensitive and specific to FAS and prenatal alcohol exposure. If the specificity falls below 95%, two fundamental problems arise. First, the diagnostic label FAS is rendered medically invalid. If you label the patient's outcome FAS, you are declaring a patient has a syndrome caused by their mother's consumption of alcohol during pregnancy.[9] But if the face is not specific to alcohol, you have no medical or scientific evidence to support this declaration of causation in an individual patient. Second, a diagnosis of FAS can no longer be made in the absence of a confirmed prenatal alcohol exposure. All current FASD diagnostic guidelines allow a

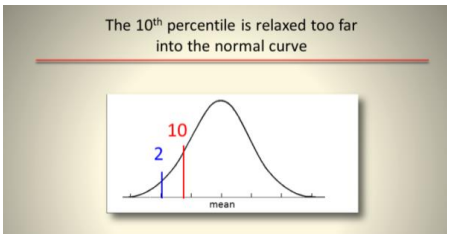
diagnosis of FAS to be rendered when prenatal alcohol exposure is unknown because the guidelines assume the FAS facial phenotype is specific to alcohol and thus can serve as confirmation of exposure. But the specificity cannot be assumed. It has to be confirmed and it has to be confirmed high. The 4-Digit Code Rank 4 face is the only FAS facial phenotype with sufficiently high specificity (>95%) to allow the outcome to be labeled FAS and allow the diagnosis to be rendered in the absence of confirmed exposure.

Two FAS/D diagnostic guidelines published subsequent to the 4-Digit Code (CDC[6] and the revised IOM[8]) relaxed the criteria for the FAS facial phenotype. Both guidelines relaxed the PFL criteria from $\leq 2^{nd}$ percentile to $\leq 10^{th}$ percentile. The revised IOM went one step further, reducing the number of required facial features from 3 to 2. Although relaxation of the criteria will reduce the specificity of the facial phenotype to FAS and prenatal alcohol exposure, neither guideline reported the specificity of their relaxed FAS facial phenotypes.

Evidence that the FAS PFL criteria should be kept at $\leq 2^{nd}$ percentile, not relaxed to $\leq 10^{th}$ percentile.

In a recently published study of 922 patients with documented prenatal exposure histories, who were evaluated by a dysmorphologist between 1978 and 2005; 1st trimester alcohol exposure correlated significantly with the presence of a smooth philtrum and thin upper lip.[48] No pattern of prenatal alcohol exposure correlated with a PFL $\leq$ 10%. The authors noted this later finding was unexpected. We too were surprised to see no correlation between short PFLs and prenatal alcohol exposure because we have always found strong correlations between these two variables. One plausible explanation for the absence of a correlation was the criterion they used to define a short PFL. The 4-Digit Code defines a short PFL as $\leq 2^{nd}$ percentile. Feldman used a more relaxed criterion; $\leq 10^{th}$ percentile. This relaxation may have relaxed the PFL too far into the normal curve (Figure 4A). To test this hypothesis, we replicated this analysis using our dataset of 1,400 patients with confirmed prenatal alcohol exposure who had undergone a FASD evaluation in the WA State FASDPN between 1993 and 2005 (Figure 4B). When the definition of a "short" PFL was relaxed to $\leq$ 10%, no correlations were found with any pattern of prenatal alcohol exposure. When the definition of a "short" PFL was set back to $\leq$ 2% (the criteria used by the 4-Digit Code), strong, significant correlations were found with quantity, frequency, and duration of alcohol exposure (Figure 4B). This provides strong evidence that the PFL criterion for the FAS facial phenotype should be set at $\leq 2^{nd}$ percentile, not relaxed to $\leq 10^{th}$ percentile.

FIG. 4AB When a short PFL is defined as ≤ 2nd percentile (as reflected in the 4-Digit Code), significant correlations are detected with prenatal alcohol exposure. When the definition is relaxed to ≤ 10th percentile (as reflected in the CDC and Revised IOM guidelines), no correlations with prenatal alcohol exposure are detected. These findings were reported by Feldman, et al[48] and replicated here using our FASDPN dataset.



A

Prenatal alcohol exposure not correlated with PFL when criteria relaxed to ≤ 10th percentile

		4-Digit PFL		CDC & Revised IOM PFL	
Prenatal Alcohol Exposure		≤ 2%	> 2%	≤ 10%	> 10%
Days / Week	n	534	324	673	185
	Mean (SD)	4.6 (2.3)	4.2 (2.4)	4.4 (2.4)	4.4 (2.4)
	F (p-value)	3.7 (.04)		.03 (.83)	
Max. Drinks / Week	n	359	222	456	125
	Mean (SD)	64.9 (92)	50.1 (59)	60.7 (86)	53.9 (60)
	F (p-value)	2.3 (.02)		.80 (.41)	
Trimesters	All 3: n (%)	533 (64)	301 (36)	661 (79)	173 (21)
	1 to 2: n (%)	203 (56)	157 (44)	267 (74)	93 (26)
Chi Square, Yates (p-value)		5.7 (.02)		3.5 (.07)	

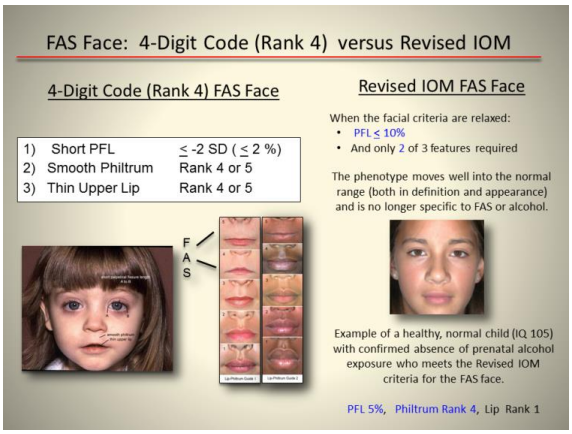
B

Evidence that the FAS facial criteria require all 3 features, not just 2 of the 3.

The Revised-IOM[8] criteria for the FAS facial phenotype relaxed the PFL to ≤ 10th percentile and requires only 2 of the 3 facial features be present. A 2006 study[23] confirmed these relaxations in the facial criteria rendered the Revised-IOM FAS facial phenotype non-specific to both prenatal alcohol exposure (specificity 75%) and FAS (specificity 68%). For reference, a specificity of 50% is equivalent to random chance; the predictive equivalent of flipping a coin. The specificity of the 4-Digit Code FAS facial phenotype to FAS and prenatal alcohol exposure is >95%. In the 2006 study, the performance of the Revised-IOM FAS criteria was assessed by applying them to two populations: 1) 952 alcohol-exposed patients evaluated in the WA FASDPN clinics, and 2) 16 healthy, high-functioning children with confirmed absence of prenatal alcohol exposure enrolled as controls in a magnetic resonance study. In this study a substantial number of patients in the FASD clinics met the Revised-IOM criteria for the full FAS facial phenotype (35%; 330 of 952 subjects), but very few of them met the Revised-IOM criteria for a diagnosis of FAS (11.8%; 39 of 330 subjects). If the Revised-IOM FAS facial phenotype were specific to FAS, then it would be expected that the vast majority of those with the FAS face would have FAS. But just the opposite was observed. The vast majority of those with the FAS face (88.2%; 291 of 330 subjects) did not

have FAS. If the Revised-IOM FAS face were specific to (caused only by) prenatal alcohol exposure, then individuals could not have the FAS face if they had not been exposed to alcohol. However, this study found that 25% of the high-functioning children with confirmed absence of prenatal alcohol exposure met the criteria for the Revised-IOM FAS face. When the facial criteria are relaxed as specified in the Revised IOM criteria, the phenotype moves well into the normal range (both in definition and appearance) and is no longer specific to FAS or prenatal alcohol exposure (Figure 5).

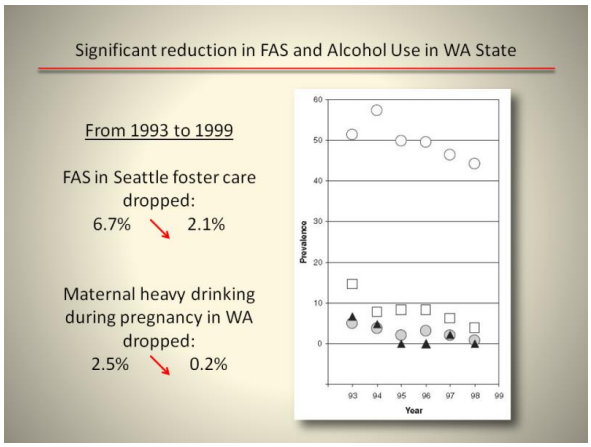
FIG. 5 When the FAS facial phenotype is relaxed[8] (photo on the right), the phenotype moves well into the normal range (both in definition and appearance) and is no longer specific to FAS or prenatal alcohol exposure.



2A.2. The Rank 4 face is so specific to FAS, it alone was used to accurately screen for FAS in a 10-year, foster care FAS screening program. This, in turn, allowed us to track the prevalence and prevention of FAS in WA State.

The high specificity of the Rank 4 FAS facial phenotype to FAS and prenatal alcohol exposure was further confirmed through a 10-year, active case-ascertainment, foster care FAS screening program conducted in Seattle.[15] If the Rank 4 FAS facial phenotype is truly highly specific to FAS and prenatal alcohol exposure, then one should be able to screen for FAS using nothing more than a facial photograph. Our 10-year foster care FAS screening program confirmed this to be true. All children entering a foster care program had their 2D digital facial photograph analyzed with the FAS Facial Photographic Analysis Software.[33,40] All children with the Rank 4 FAS facial phenotype were classified as screen-positive for FAS and received an interdisciplinary FASD diagnostic evaluation using the 4-Digit Code. The screening tool (presence of the Rank 4 FAS facial phenotype in a 2D facial photograph) performed with 100% sensitivity, 99.8% specificity, 85.9% predictive value positive and 100% predictive value negative for FAS. Over 2,500 children were screened over a period of 10 years (1999-2009) with 98% participation. This 10 year active-case-ascertainment screening program confirmed 1/100 children in foster care in the Seattle area had FAS. Data from this study would go on to confirm that the prevalence of FAS in this foster care population decreased significantly (6.7% to 2.1%)[24,34] (across successive birth cohorts) as the prevalence of heavy maternal drinking during pregnancy in WA State decreased significantly (2.5% to 0.2%) in those same years[24] (Figure 6).

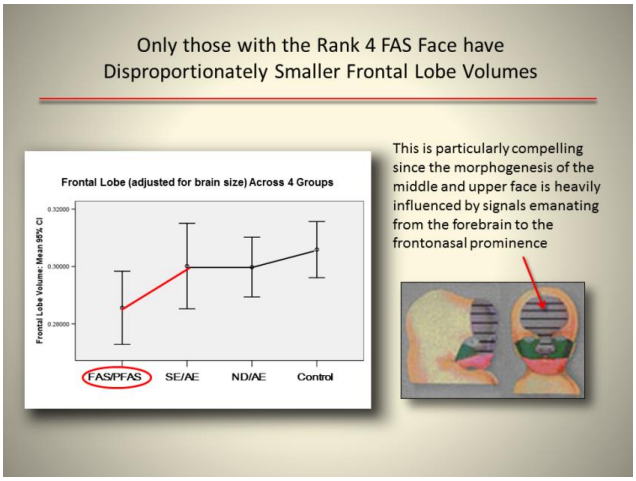
FIG. 6 The prevalence of FAS dropped significantly from 6.7% to 2.1% among children in Seattle foster care born between 1993 and 1999. This correlated with a significant decline (2.5% to 0.2%) in the prevalence of women drinking during pregnancy in WA State during those same years[24]. Key: Decline in the prevalence of alcohol use by women in Washington State from 1993 to 1998: (○) Any level of alcohol use 3 months prior to pregnancy; (□) Any level of alcohol use in the third trimester of pregnancy; (●) Heavy alcohol use (>14 drinks/week) 3 months prior to pregnancy.[34] (▲) Prevalence of FAS among children in a Seattle foster care program born from 1993 to 1998.[24]



2A.3. Individuals with the Rank 4 FAS face have significantly and disproportionately smaller frontal lobe volumes. This is particularly compelling since the forebrain plays an important role in the normal morphogenesis of the midline facial features and laboratory studies of alcohol teratogenesis report midventral forebrain deficiencies associated with facial dysmorphia in both mice and primates.

In an MRI study comparing brain volumes among children with 4-Digit Code diagnostic classifications of FAS/PFAS, SE/AE, and ND/AE, and a healthy, unexposed control group, the mean volume of the frontal lobe was significantly and disproportionately smaller in the FAS/PFAS group compared with each of the other groups.[16] (Figure 7). The FAS/PFAS group was the only group with the full Rank 4 FAS facial phenotype. This is a particularly compelling and validating finding when one considers the morphogenesis of the middle and upper face is heavily influenced by signals emanating from the forebrain to the frontonasal prominence.[49] The correlation between median facial malformations and underlying brain malformation has been known for decades.[50] The FAS facial features (short palpebral fissure lengths, a smooth philtrum and a thin upper lip) are midline anomalies derived from the anterior frontal neural crest primordia of the early forebrain.[51] Deficiencies in the numbers of crest cells most frequently affect development of the frontonasal derivatives and are usually associated with defective forebrain and eye development.[51] It has long been speculated that some extreme forms of midline facial anomalies (i.e., cyclopia, holoprosencephaly, arhinencephaly) are pathognomonic of brain malformation.[50] This speculation was further supported by the presence of a proportional increase in midventral forebrain deficiencies and the severity of facial dysmorphia in mice[52-54], nonhuman primates[29,55], and now humans.[16]

FIG. 7 The mean volume of the frontal lobe was significantly ($p < 0.05$) and disproportionately smaller in the FAS/PFAS group compared with each of the other study groups (SE/AE, ND/AE and unexposed healthy controls).[16] The FAS/PFAS group is the only group with the full FAS facial phenotype. Morphogenesis of the middle and upper face is heavily influenced by signals emanating from the forebrain to the frontonasal prominence.[49] The frontonasal prominence is the striped region in the insert depicting a 5-week (left) and 10-week (right) fetus.[56]



2A.4. The high specificity of the Rank 4 FAS facial phenotype is quintessential to the validity of all diagnoses under the umbrella of FASD, not just those labeled FAS.

Why are the criteria used to define the FAS facial phenotype so important to the medical validity of all diagnoses under the umbrella of FASD, not just the diagnosis of FAS? When one makes a diagnosis of FAS, one is stating implicitly that the individual has a syndrome caused by prenatal alcohol exposure.[9] One is also stating implicitly that the biological mother drank alcohol during pregnancy and, as a result, harmed her child. These are bold conclusions to draw and are not without medical, ethical, and even legal consequences. What happens when the FAS face is not at least 95% specific to FAS and prenatal alcohol exposure? The whole FASD diagnostic system collapses like a house of cards. Here is why.

a. The term FAS is rendered invalid. If the face is not specific to (caused only by) alcohol, it is no longer medically valid or medically ethical to label the condition fetal alcohol syndrome. You can no longer confirm alcohol is causally linked to any of the outcomes (growth, brain, or face) in an individual patient.
b. The diagnosis FAS/alcohol-exposure-unknown is also rendered invalid. If the face is not specific to (caused only by) alcohol, the FAS face can no longer serve as the confirmation of alcohol exposure when the exposure history is unknown.
c. FAS is no longer distinct from ARND. ARND is "FAS without the face". But if there is no FAS face, there is no distinction between FAS and ARND. Thus, you can no longer justify classifying FAS and ARND separately.
d. The term "ARND" remains invalid. Since ARND has no feature specific to prenatal alcohol, you are in no position to declare the Neurodevelopmental Disorder is "Alcohol-Related" (ARND) in an individual patient. This is discussed more fully below.

2B. Principle 2: The FAS facial phenotype presents along a clinically meaningful continuum.

2B.1. The FAS facial phenotype is not just present or absent. It presents along a continuum that is significantly correlated with (predictive of) abnormal brain structure and function.

The more severe the FAS face, the more severe the CNS structural/functional abnormality (Figure 8); growth deficiency (Figure 9), and duration of alcohol exposure (Figure 10).[9,26,27] We predicted back in 1999[29] that if the FAS facial phenotype was measured on a continuum, it would serve as a more sensitive indicator of teratogenic outcome than the previous practice of recording the FAS facial phenotype as simply present or absent as documented in the IOM FASD guidelines.[5] Figures 8 and 9 clearly confirm this to be true. The statistically significant linear correlations observed between the magnitude of expression of the FAS facial phenotype and brain structure and function: 1) further validate that short PFLs, a smooth philtrum, and a thin upper lip are the key diagnostic facial features, 2) are consistent with the clinical literature that midline facial defects predict underlying brain dysfunction[4,25,29,30,47,50], and 3) provide evidence that an intermediate expression of the FAS facial phenotype serves as an important clinical risk factor for brain damage caused by prenatal alcohol exposure. This continuum is important in predicting the risk for CNS dysfunction among young children who present with some or all of the FAS facial features, but are too young to engage in a comprehensive assessment of brain function.[9] The correlations between face and brain (Figure 8) also demonstrate that individuals with the full FAS facial features do have CNS structural and functional abnormalities that are significantly more severe than individuals with milder expressions of the FAS facial phenotype.[16] This is not an artifact of the criteria used to define the different FASD diagnostic subgroups. In accordance with the 4-Digit Code, FAS/PFAS and SE/AE must meet the same diagnostic threshold for severe dysfunction (CNS Rank 3 and/or 4). That said; those who meet that threshold and have the FAS facial phenotype (FAS/PFAS) have significantly more severe dysfunction, on average, than those who meet that threshold and do not have the FAS facial phenotype (SE/AE) (Fig 17). Not all published studies identify statistically significant contrasts in CNS abnormality between alcohol-exposed individuals with and without the FAS facial phenotype. This may be a reflection of the criteria used to define the FAS facial features in those studies.[57-60] We too failed to observe any correlation between face and brain when we used less rigorous methods of defining and measuring the face (e.g., the gestalt FAS facial phenotype) prior to the establishment of the 4-Digit Code.[4] When the facial criteria of the 4-Digit Code are used, significant contrasts are observed between alcohol-exposed groups with and without the FAS facial phenotype.[61]

FIG. 8 Data from the WA FASDPN clinics[26] and the MRI studies[16] confirm that the more severe the FAS facial phenotype (4-Digit Code Facial Rank 1 = no features, 2 = mild features; 3 = moderate features; 4 = severe features, presented on the x axis) the more severe the abnormalities in CNS structure and function (FSIQ; head circumference centile; visual motor integration standard score; Quick Neurological Screen Test score; prevalence of significant developmental delay; and number of significantly impaired domains of function, presented on the y axis). These statistically significant linear correlations serve to validate the 4-Digit Code FAS facial phenotype.

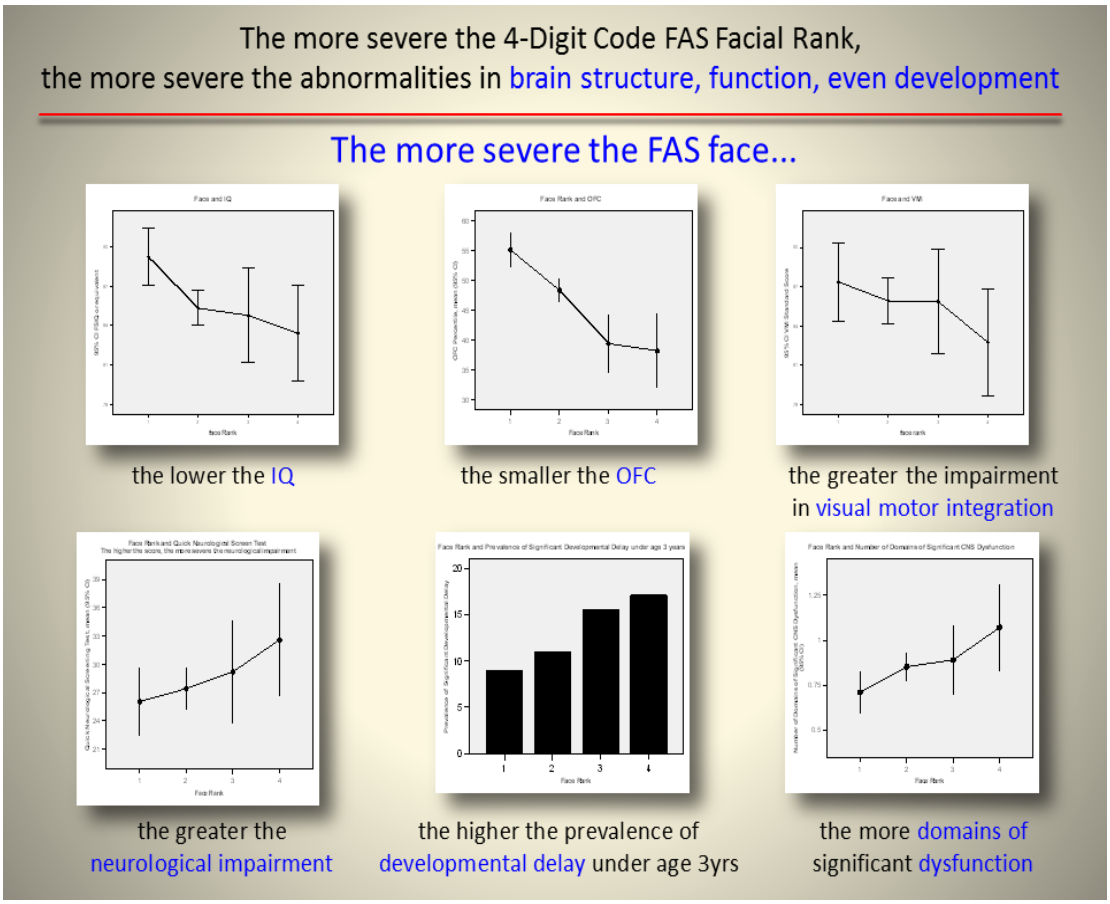


FIG. 9. Data from the WA FASDPN clinics[26] document the more severe the 4-Digit FAS facial phenotype (Facial Ranks 1-4), the more severe the growth deficiency (birth weight and length percentiles as well as weight and height percentiles at the time of the FASD diagnostic evaluation. Pictured are statistically significant linear trends.

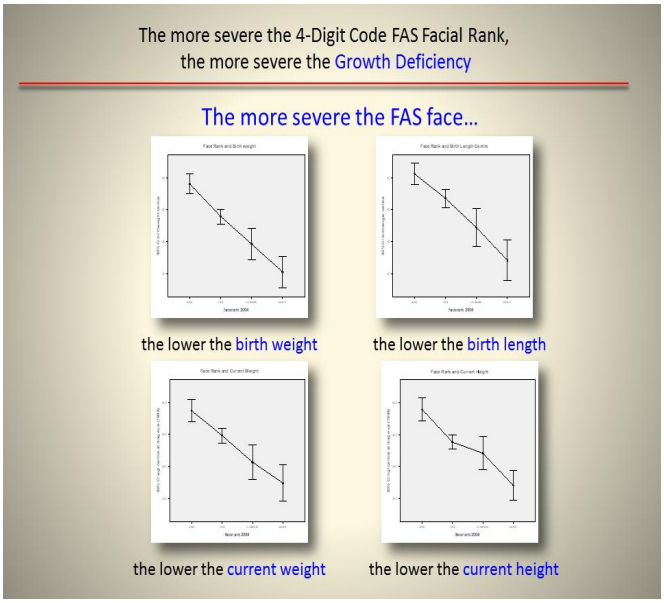
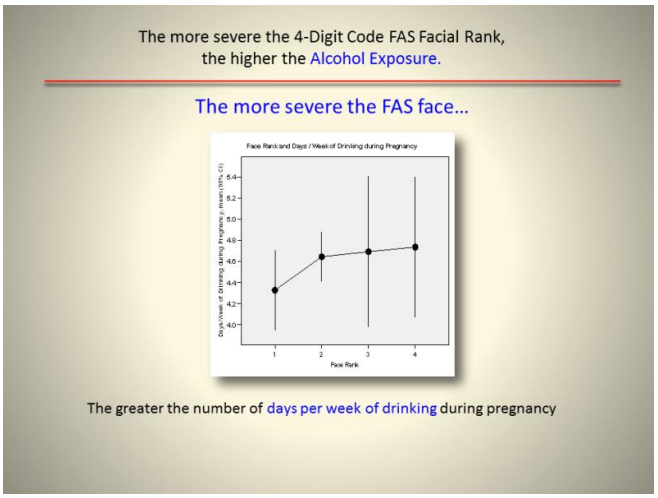


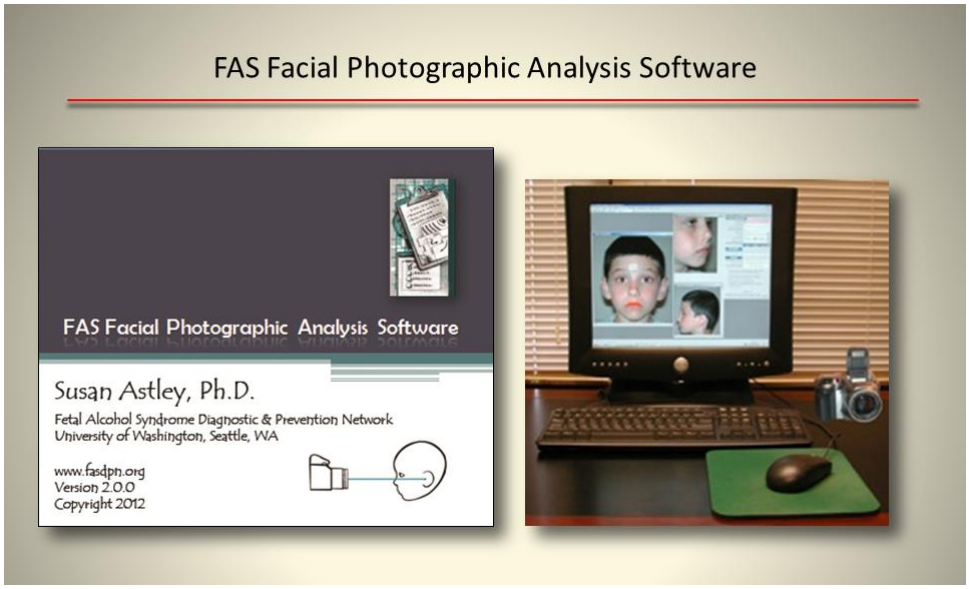
FIG. 10 Data from the WA FASDPN clinics[26] document the more severe the 4-Digit FAS facial phenotype (Facial Ranks 1-4), the greater the number of days/week of drinking during pregnancy (significant linear trend, F=10.7, p = 0.001).



2B.2. The FAS facial features can be accurately measured from a 2D digital photo using the FAS Facial Photographic Analysis Software.

The full continuum of the FAS facial features can be easily and accurately measured from 2D digital facial photographs using the FAS Facial Photographic Analysis Software.[33,40] (Figure 11). This Windows-based software is both inexpensive ($60 USD) and User friendly. This ease, accuracy, and low cost of measurement are why a 2-dimentional (2D) format was selected over a 3D format back in 2004. This software has been used to measure and diagnostically classify the facial features of all patients (> 2,550) evaluated in the WA State FASD clinics over the past 20 years.[26] It was also used to screen over 2,000 children participating in a 10-year foster care FAS screening program in Seattle.[15] The software was used to generate the Canadian PFL normal growth charts in 2010.[62] These Canadian PFL charts were subsequently incorporated into Version 2.0 of the software in 2012.[33] The software is currently in use worldwide. A video demonstration of the software is posted on the FASDPN website.

FIG. 11 The FAS Facial Photographic Analysis Software (Version 2.0)[33] is a Windows-based program that provides accurate measurement of FAS facial features from a 2D digital facial photograph. The software has been distributed worldwide since 2004.

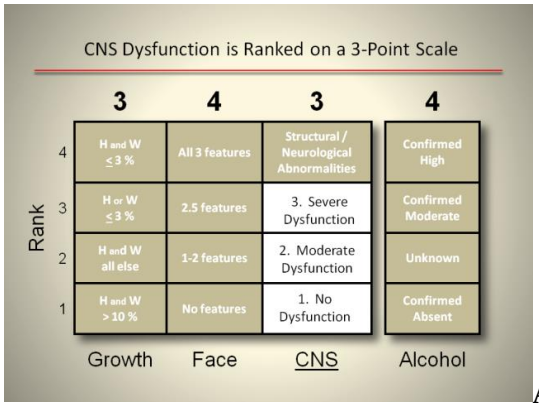


3. The 4-Digit Code's method for case-defining the highly variable CNS dysfunction that typifies FASD demonstrates high construct validity.

3A. The 4-Digit Code's method for classifying CNS dysfunction (CNS Ranks 1, 2, and 3) successfully predicts underlying CNS structural abnormality as it was designed to do.

An important contribution of the 4-Digit Code was the method used to case-define the highly variable, nonspecific CNS dysfunction that typifies FASD. It was important to establish a method that quantified the breadth and magnitude of dysfunction (e.g., the number of domains of function 2 or more SDs below the mean as measured by standardized psychometric tools administered by a clinician) without unduly constraining which domains must be impaired. CNS dysfunction is ranked on a 3-Point likert scale (Figure 12A). Ranks 1, 2, and 3 reflect none, 1 to 2, and 3 or more domains of dysfunction respectively. The 3 CNS Ranks in the 4-Digit Code were case-defined to predict increasing likelihood of underlying structural brain abnormality[4,9,16,26] (Figure 12B). Alcohol is a teratogen that interferes with the structural development of the fetal brain. This, in turn, can lead to abnormal function. We postulated in 1997… "*The greater the dysfunction, the higher the probability of underlying structural brain abnormality*".[1] In 2009, our MRI study confirmed this to be true![16] Many significant correlations were identified between CNS dysfunction and brain region volumes, but perhaps most striking was the significant, inverse, linear correlation between increasing CNS dysfunction (CNS Ranks 1,2 and 3) and decreasing caudate volume (Figure 12C). This is powerful evidence (construct validity) that the CNS Ranking system used by the 4-Digit Code is clinically and scientifically valid.

FIG. 12 A. The 4-Digit Code ranks CNS dysfunction on a 3-point scale (none, moderate, severe). B. The 3 CNS Ranks were case-defined to predict increasing likelihood of underlying structural brain abnormality.[4] C. MRI confirmed this to be true.[16] The more severe the CNS dysfunction (Rank 1, 2, 3), the smaller the caudate volume (significant linear trend F=13.5; p<.001; Duncan range test confirms each CNS group is significantly distinct from the others).



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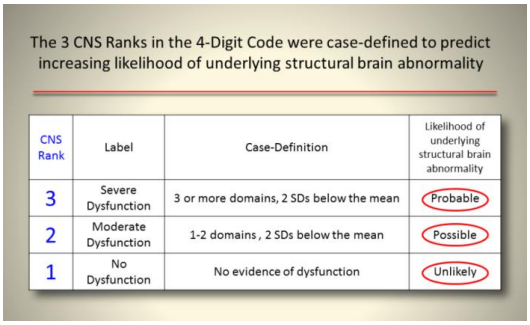

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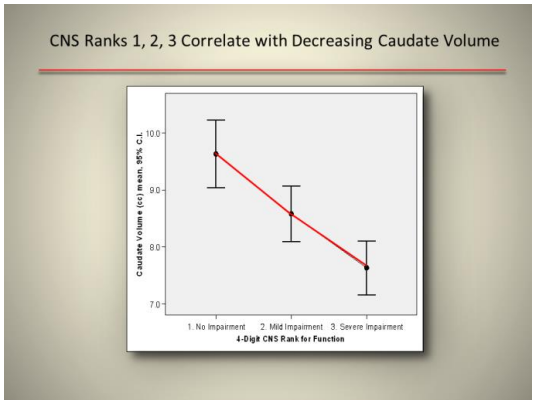

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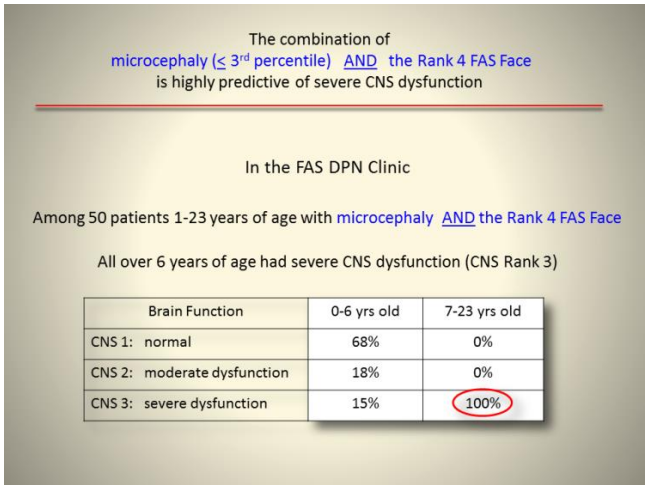
3B. Microcephaly predicts severe CNS dysfunction among infants/toddlers who present with the full Rank 4 FAS facial phenotype.

One area of discordance between current FASD diagnostic guidelines is the CNS criteria for FAS.[9] Some guidelines allow microcephaly alone to meet the CNS criteria, some guidelines do not. If severe functional abnormality is required, a diagnosis of FAS cannot be rendered in a child who is too young (typically < 6 years old) to participate in a comprehensive assessment of function (IQ, language, memory, executive function, etc). Is it clinically cogent to render a diagnosis of FAS in an infant who presents with structural evidence of CNS abnormality (microcephaly), but is too young to assess and confirm the presence of CNS dysfunction? Is the presence of microcephaly (an occipital frontal circumference (OFC) 2 or more SDs below the mean) in an infant with the Rank 4 FAS facial phenotype predictive of brain dysfunction that will not be revealed until the infant is old enough to participate in higher level functional assessments? The answers to both questions are yes.[9,26] In a cross sectional look at the first 1,400 patients evaluated in the WA FASDPN, 154 patients were diagnosed with FAS/PFAS.[26] Of the 154 patients, 69 (44.8%) had microcephaly. Of the 69 with microcephaly, 36 (52%) had no evidence of brain dysfunction (Rank 1), 14 (20%) had moderate (Rank 2) brain dysfunction, and 19 (28%) had severe (Rank 3) brain dysfunction. Did the 52% with no evidence of brain dysfunction, truly have normal function, or were they too young to accurately/comprehensively assess function? The data would suggest they were too young to assess. The subset with no evidence of brain dysfunction (Rank 1) had a mean age of 4.7 (6.0 SD) years. The subset with Rank 2 moderate dysfunction had a mean age of 7.5 (5.9 SD) years. And the subset with Rank 3 severe dysfunction had a mean age of 10.3 (5.9 SD) years. The older the patient, the more likely they revealed evidence of moderate to severe dysfunction (ANOVA F=5.8 (df 2), p=.005). Another way to look at this using our current dataset of 2,550 patients with FASD is as follows. Of all 50 patients, 1-23 years of age, who presented with microcephaly and the Rank 4 FAS facial phenotype, only 15% of the group $\leq$ 6 years of age presented with severe dysfunction (CNS Rank 3), but 100% > 6 years of age had severe CNS dysfunction (Figure 13). These analyses strongly support that rendering a diagnosis of FAS in a newborn/infant that presents with microcephaly, but is too young to assess/confirm brain dysfunction, is clinically sound. The combined presence of the Rank 4 FAS facial phenotype, microcephaly ($\leq 3^{rd}$ percentile), and prenatal alcohol exposure are highly predictive of brain dysfunction. The significant linear correlations between increasing magnitude of expression of the 4-Digit FAS facial phenotype and 1) increasing CNS dysfunction, and 2) decreasing head circumference further support this (Figure 8). Children with FAS are born with FAS. Early diagnosis affords early intervention. Postponing an FAS diagnosis in children with microcephaly, who were not old enough to participate in higher-level functional assessments, could lead to missed opportunities for early intervention.[63]

FIG. 13 Is microcephaly a sufficient measure of brain abnormality in children too young to assess for brain dysfunction? Data from the WA FASDPN clinics confirm that the combination of microcephaly and the Rank 4 FAS facial phenotype in children ≤ 6 years old is highly predictive of severe CNS dysfunction that will be evident later in childhood/adolescence once they are old enough to assess.



4. The 4-Digit Code generates four distinct diagnostic subgroups (FAS, PFAS, SE/AE, and ND/AE) under the umbrella of FASD.

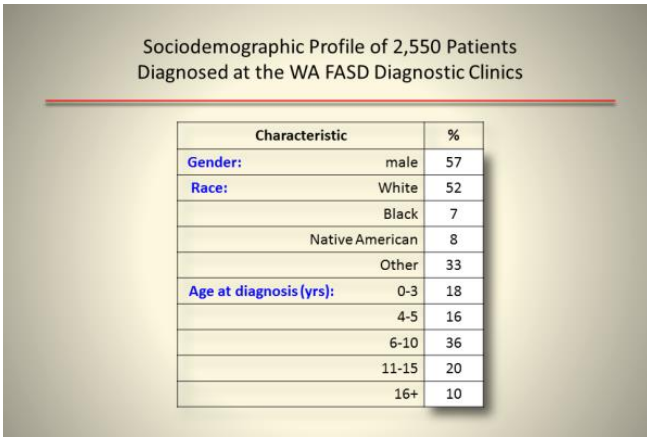
4A. FAS, PFAS, SE/AE and ND/AE are clinically distinct diagnostic subgroups that span the full continuum of FASD:

The WA FASDPN clinics have conducted FASD diagnostic evaluations on 2,550 patients with prenatal alcohol exposure over 20 years (Figures 2, 14).[26] They range in age from newborn (2 days old) to adult (53 years old), with the vast majority being school-aged. The 4-Digit Code produces diagnostic subgroups (FAS, PFAS, SE/AE, and ND/AE) that are confirmed to be clinically and statistically distinct.[9,16,26,27,35] (Figures 14-17). For example, FAS presents with growth deficiency (height and/or weight ≤ 10th percentile); PFAS does not. Only FAS/PFAS have the FAS facial phenotype, significantly ($p < 0.05$) smaller frontal lobe volumes[16] (Fig 15a), and reduced choline neurometabolite levels[35] (Fig 16). Only FAS/PFAS and SE/AE (the only two groups with severe CNS dysfunction (Ranks 3) have significantly ($p < 0.05$) smaller caudate volumes.[16] (Fig 15b). FAS/PFAS have, on average, more severe CNS structural and functional abnormalities than SE/AE even though FAS/PFAS and SE/AE must meet the same diagnostic threshold for severe dysfunction (CNS Rank 3 or 4).[16] (Figures 15, 17). Those who meet that threshold and have the FAS facial phenotype (FAS/PFAS) have more severe outcomes than those who meet that threshold and do not have the FAS facial phenotype (SE/AE). SE/AE has more severe CNS dysfunction than ND/AE (Figures 15). SE/AE have more severe CNS dysfunction and a higher prevalence of CNS structural abnormalities (58%) than ND/AE. And 43% of ND/AE have, on average, one or more significantly small brain region volumes, despite their more moderate CNS dysfunction.[16] (Figure 15c).

Although functional impairment typically becomes more severe as one advances from ND/AE to SE/AE to FAS/PFAS, the one domain that is comparably and significantly impaired

across all diagnostic subgroups is adaptive function.[26] (Figure 18). Not only are the diagnostic subgroups distinct based on standardized measures of CNS structure and function, even caregivers can distinguish between these diagnostic subgroups.[26] (Figure 19). A structured 2-hour interview is conducted with the caregivers by the medical doctor paired with the psychologist or social worker. The 4-Digit Code Caregiver Interview Form (p.6 of the Diagnostic Form[3]) is used. The interview takes place before a diagnosis has been rendered and before the clinicians have even met the child. Thus the results are not biased. The outcomes presented in Figure 19 serve to validate the clinical utility of the semi-structured caregiver interview developed and used by the 4-Digit Code.

FIG. 14. A) Sociodemographic profile and B) distribution of FASD 4-Digit Code diagnostic outcomes of the 2,550 patients with prenatal alcohol exposure evaluated in the WA FASDPN Clinics over the past 20 years.



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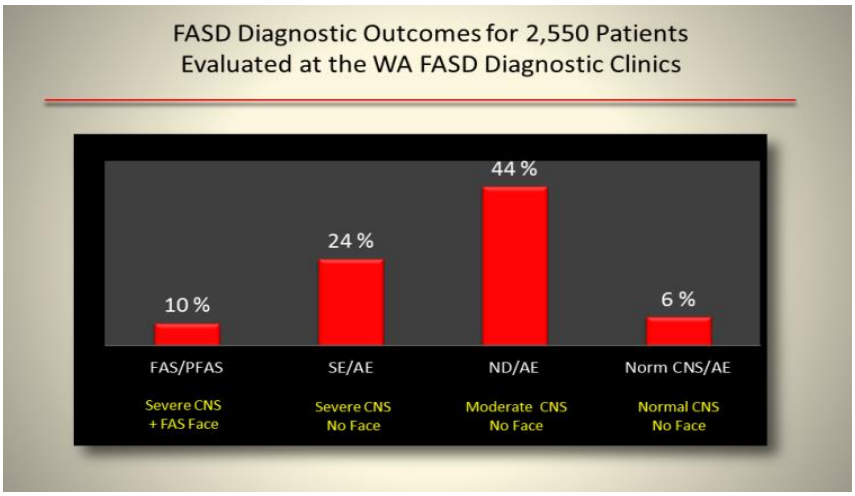

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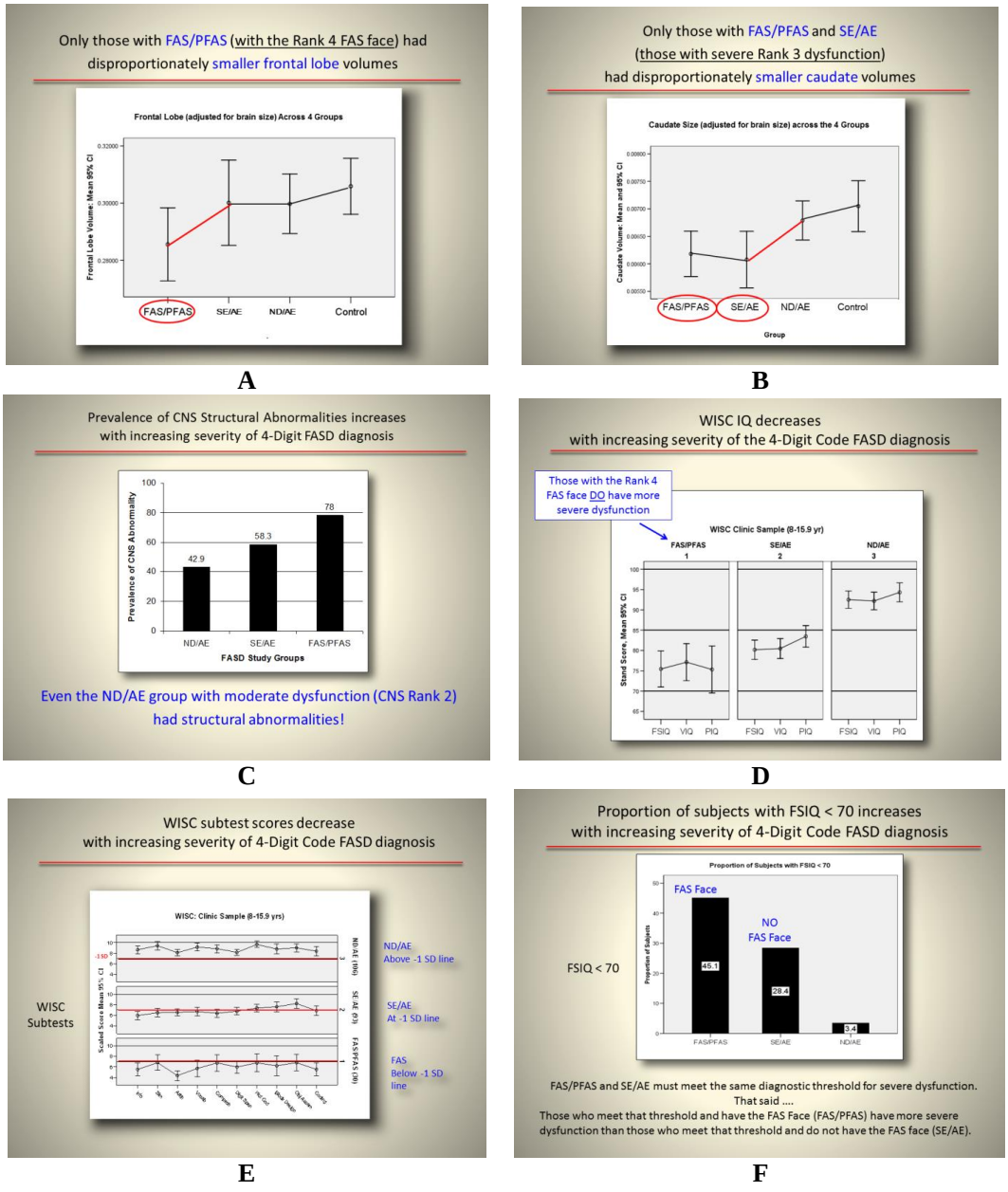
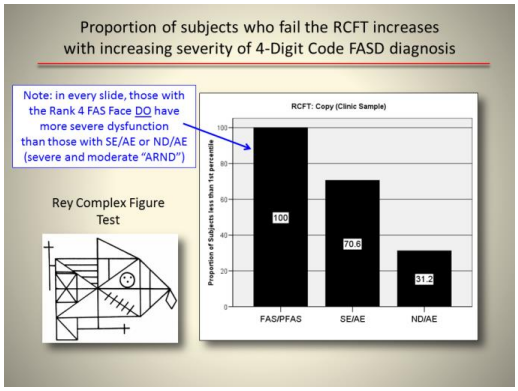
FIG. 15 FAS, PFAS, SE/AE, and ND/AE are clinically and statistically distinct diagnostic subgroups that span the full continuum of FASD. Individuals with the FAS facial phenotype (FAS/PFAS) have more severe CNS dysfunction than individuals without the facial phenotype (SE/AE).



Validation of the fetal alcohol spectrum disorder (FASD) 4-Digit Diagnostic Code



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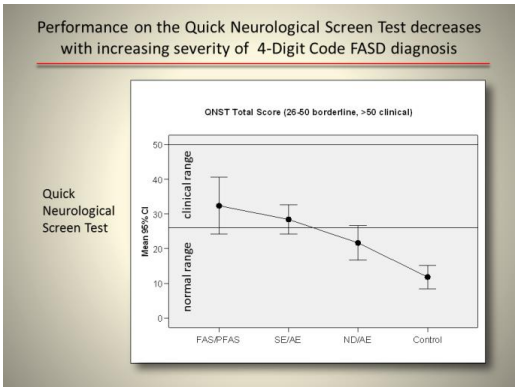

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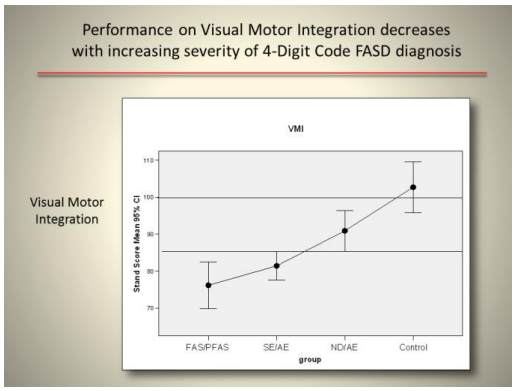

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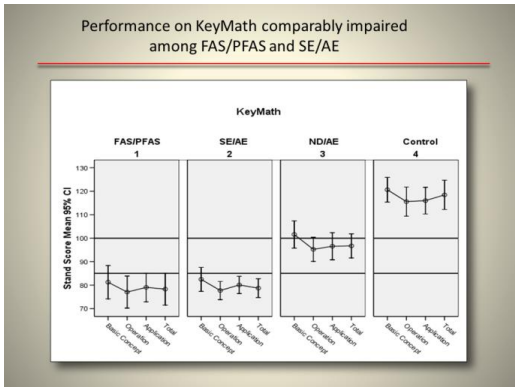

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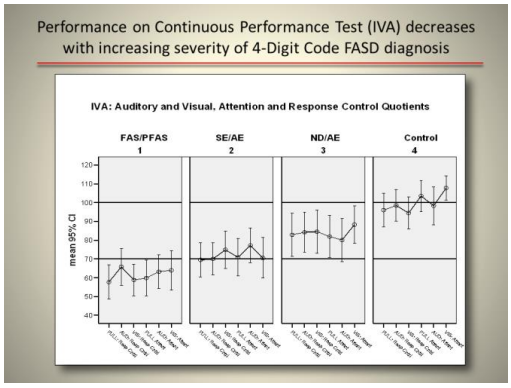

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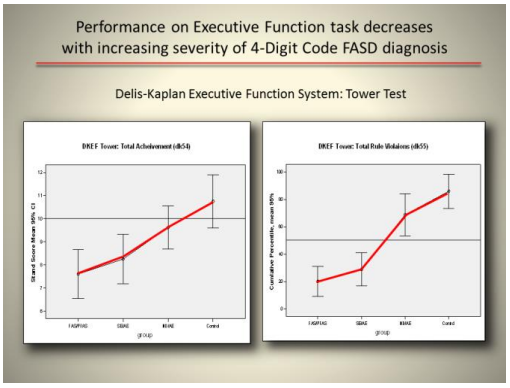


L

FIG. 16 An MRS study[35] confirmed the neurometabolite choline was significantly ($p<0.05$) lower among the FAS/PFAS group and significantly ($p<0.05$) lower among those with longer durations of prenatal alcohol exposure.

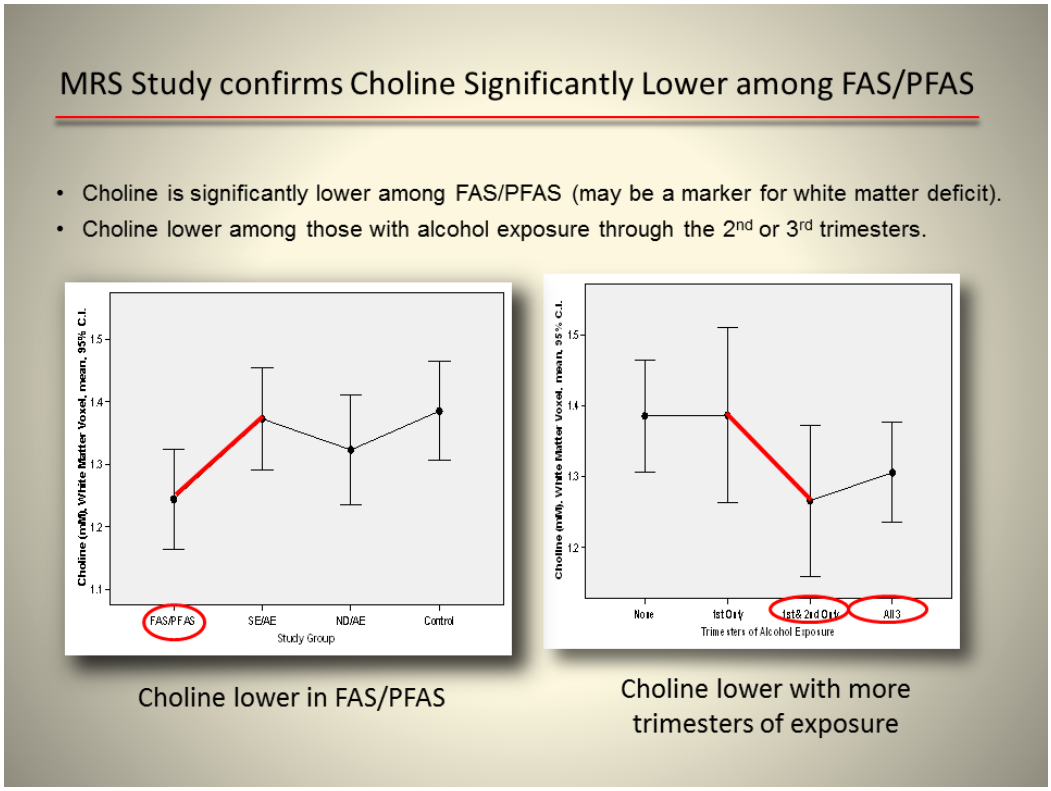
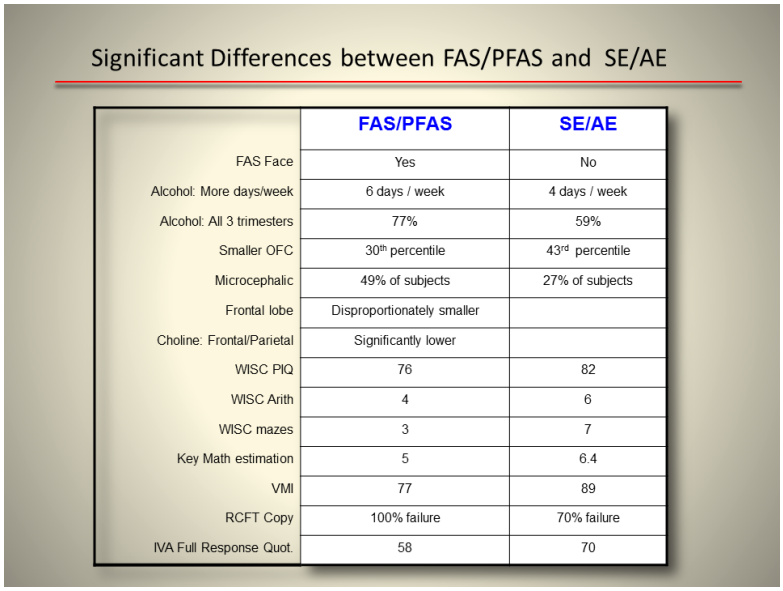


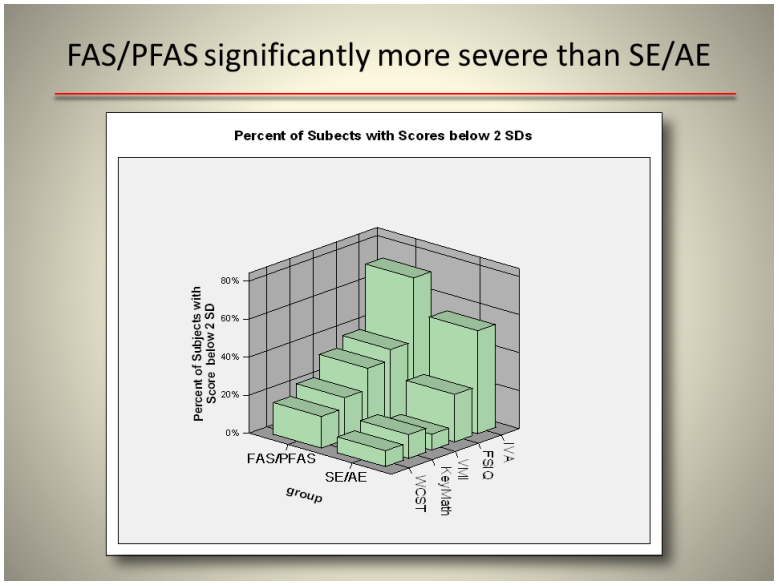
FIG. 17 Despite the fact that the CNS diagnostic criteria for FAS/PFAS and SE/AE are identical (CNS Ranks 3 and/or 4), those who meet that threshold and have the FAS facial phenotype (FAS/PFAS) have significantly more severe CNS abnormalities than those who meet that threshold and do not have the FAS facial phenotype (SE/AE).[16,26] A. Tabular presentation. B. Graphical presentation.



Significant Differences between FAS/PFAS and SE/AE

	FAS/PFAS	SE/AE
FAS Face	Yes	No
Alcohol: More days/week	6 days / week	4 days / week
Alcohol: All 3 trimesters	77%	59%
Smaller OFC	30th percentile	43rd percentile
Microcephalic	49% of subjects	27% of subjects
Frontal lobe	Disproportionately smaller	
Choline: Frontal/Parietal	Significantly lower	
WISC PIQ	76	82
WISC Arith	4	6
WISC mazes	3	7
Key Math estimation	5	6.4
VMI	77	89
RCFT Copy	100% failure	70% failure
IVA Full Response Quot.	58	70

A



B

FIG. 18 Although functional impairment typically becomes more severe as one advances from ND/AE to SE/AE to FAS/PFAS, the one domain that is comparably and significantly impaired across all diagnostic subgroups is adaptive function.[26]

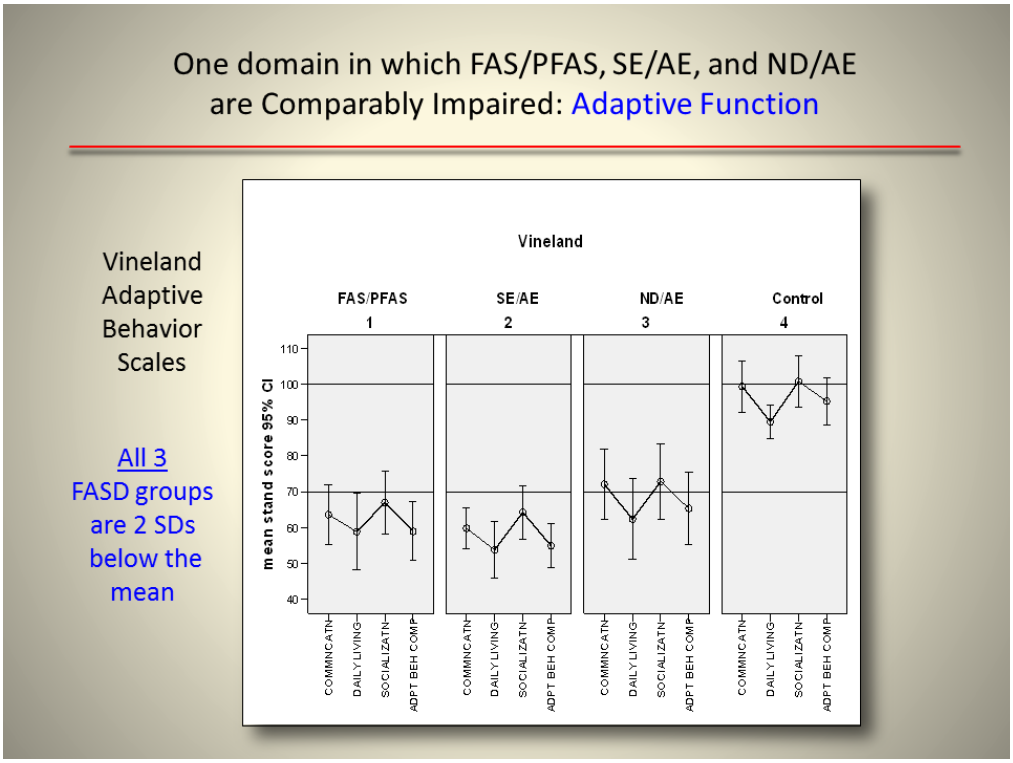
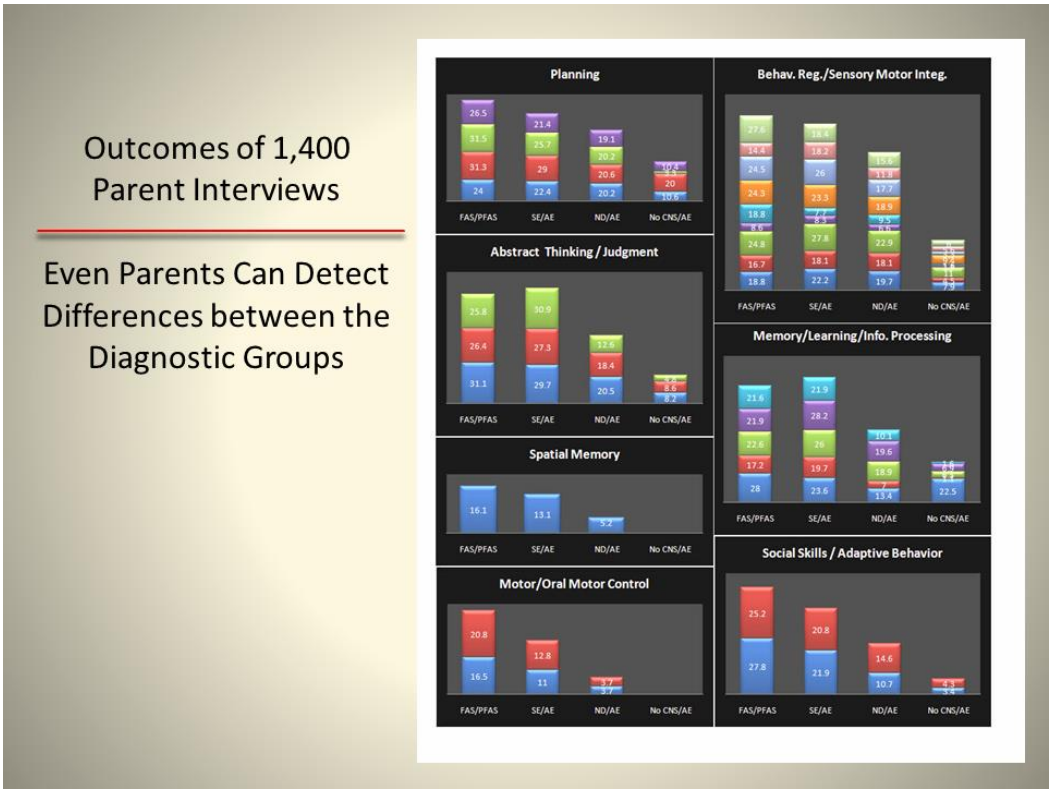


FIG. 19 Even caregivers can detect behavioral differences between the 4-Digit Code Diagnoses FAS/PFAS, SE/AE, and ND/AE.[26] A structured 2-hour interview is conducted with the caregivers by the medical doctor and psychologist using the 4-Digit Code Caregiver Interview Form (p.6 of the Diagnostic Form). The higher the bar, the more severe the child's behavioral problem reported by the caregiver.



4B. Extensive evidence supports the inclusion of individuals with moderate dysfunction (ND/AE) under the umbrella of FASD.

Prenatal alcohol exposure causes the full spectrum of CNS dysfunction from moderate to severe.[17,26,64] Individuals that present with CNS dysfunction, but no physical features of FAS, are often referred to as having Alcohol-Related Neurodevelopmental Disorder (ARND).[5] The Canadian[7] and Revised IOM[8] guidelines use the term ARND to classify individuals who present with severe CNS dysfunction. Neither guideline includes a diagnostic category for individuals that present with moderate dysfunction. In contrast, the 4-Digit Code[3] has two diagnostic categories to capture the full spectrum of dysfunction: 1) Neurobehavioral Disorder/Alcohol Exposed (ND/AE) for moderate dysfunction (CNS Rank 2), and 2) Static Encephalopathy/Alcohol Exposed (SE/AE) for severe dysfunction (CNS Ranks 3 and/or 4). The evidence that supports inclusion of ND/AE (moderate dysfunction) under the umbrella of FASD is as follows. First, and most importantly, thousands of laboratory-based studies, including our nonhuman primate studies[65,66], confirm prenatal alcohol exposure causes moderate dysfunction. Not only does it cause moderate dysfunction, but moderate dysfunction is the most common outcome. Of the

2,550 alcohol-exposed patients evaluated at the WA FASDPN clinics over the past 20 years, 44% met the criteria for ND/AE[26] (Figure 20). ND/AE was the most common outcome, exceeding the prevalence of FAS/PFAS (10%) and SE/AE (24%) combined. It is important to note that alcohol is not the only risk factor contributing to adverse outcomes in our patient population.[26] (Figure 21). So what would the diagnostic distribution look like if alcohol was the only risk factor? To answer that question, we applied the 4-Digit Code to the outcomes observed in our primate model of FASD[66] (Figure 20). Remarkably, the distribution of FAS/PFAS (4%), SD/AE (30%) and ND/AE (57%) was near identical to that observed in our FASD clinical population with ND/AE being the most common outcome. And just like in our primate model, individuals with ND/AE have alcohol exposures as high as those with FAS/PFAS and SE/AE.[26] (Figure 22). Are these moderate impairments in brain function associated with underlying CNS structural abnormalities? Again, the answer is yes. Our MRI study confirmed at least 43% of individuals with ND/AE have significant CNS structural abnormalities.[16] (Figure 15C). Our extensive experience in the WA FASDPN confirms that it is the children with moderate dysfunction that fair the worst and are often in most need of diagnostic identification and intervention. These are the children that typically slip through the cracks. Their disabilities are often not severe enough in the cognitive domain to qualify them for services (only 3% have an IQ less than 70)[26], but severe enough across many other domains (Figure 23) to adversely impact their ability to fully engage in school and live productive, independent lives. Children with ND/AE received as many intervention recommendations as children with FAS/PFAS and SE/AE.[67] (Figure 24) and caregivers reported the interventions worked as well for their children as did caregivers of children with FAS/PFAS and SE/AE.[26] (Figure 31). It is important to clarify that, when we report above that there is extensive evidence to support inclusion of ND/AE under the umbrella of FASD, we are not stating that all individuals who meet the criteria for ND/AE have FASD. By definition all individuals with Fetal Alcohol Spectrum Disorder have a disorder caused, at least in part, by their prenatal alcohol exposure. But not all individuals with ND/AE necessarily have a FASD. Only the subset of individuals whose neurobehavioral disorder was caused, at least in part, by their prenatal alcohol exposure, have a FASD. This is a current inherent weakness in the umbrella term FASD. In the absence of a biomarker that can causally link an individual's alcohol exposure with their neurodevelopmental disorder, there is no way to identify which individuals with ND/AE have FASD. This same argument applies to the diagnostic classification of SE/AE and ARND. Not all individuals who meet the criteria for SE/AE (or meet the criteria for ARND using the IOM or Canadian Guidelines) necessarily have FASD. Only the subset of individuals whose CNS abnormalities were caused, at least in part, by their prenatal alcohol exposure has FASD. And once again the field of FASD currently has no way (no biomarker) to identify this subset. Until such a biomarker is identified, if such a biomarker exists, the 4-Digit Code elects to label these categories with terms that do not imply causality.

FIG. 20 Individuals with moderate dysfunction (ND/AE) make up the majority of patients (44%) seen in the WA FASDPN clinics. Alcohol is capable of causing moderate dysfunction, as demonstrated in our primate study of alcohol teratogenicity.[66] When the 4-Digit Code was applied to the outcomes in the primate study, ND/AE was the most prevalent outcome (57%). The distribution of diagnostic outcomes observed in the primate study were near identical to the distribution observed in our clinical population.

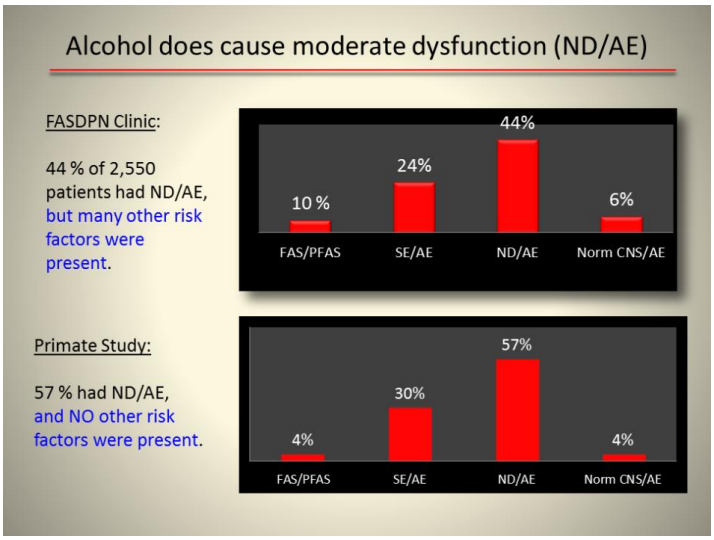


FIG. 21 Alcohol is never the only risk factor for abnormal development in a FASD clinical population. The prevalence of other risk factors among the 2,550 patients evaluated at the WA FASDPN clinics is substantial.[26]

Risk Factors Among 2,550 FASD Patients	
Prenatal alcohol exposure	100%
No prenatal care	31 %
Maternal learning disabilities	36 %
Other adverse prenatal exposures	93 %
Prenatal tobacco	62 %
Prenatal crack/cocaine	37 %
Perinatal difficulties	53 %
Foster/adoptive care	85 %
Physical abuse	34 %
Sexual abuse	24 %
Neglect	64 %
Home placements (average #)	3

FIG. 22 Among the first 1,400 alcohol-exposed patients evaluated in the WA FASDPN clinics, those with moderate CNS dysfunction (ND/AE) had alcohol exposures as high as those with severe CNS dysfunction (FAS/PFAS and SE/AE).[26]

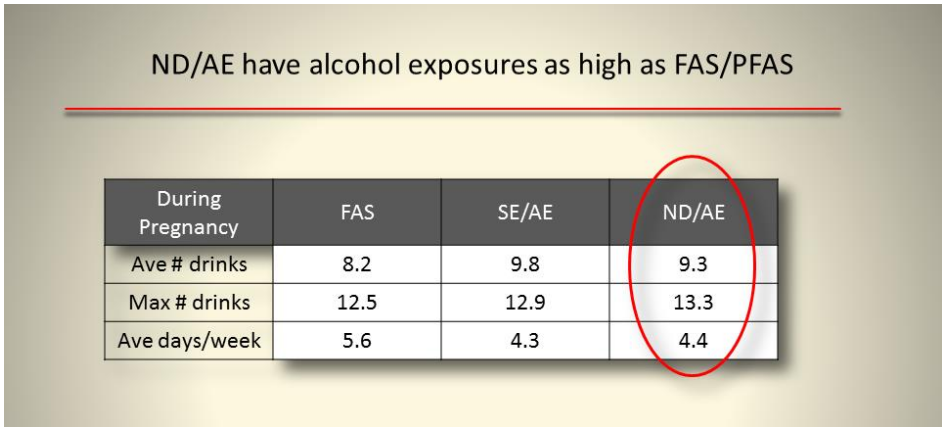


FIG. 23 Although individuals with ND/AE have less severe CNS dysfunction than FAS/PFAS or SE/AE, their disabilities span the full continuum. Their disabilities are often not severe enough in the cognitive domain to qualify them for services (only 3% have an IQ less than 70)[26], but severe enough across many other domains to adversely impact their ability to fully engage in school and live productive, independent lives.[26]

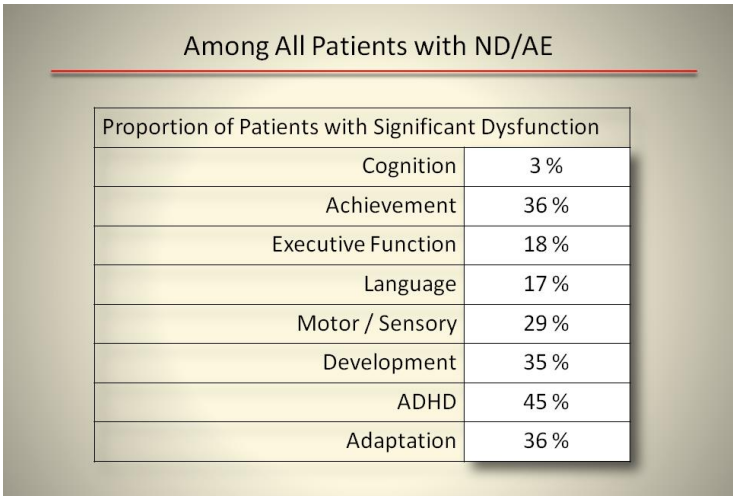
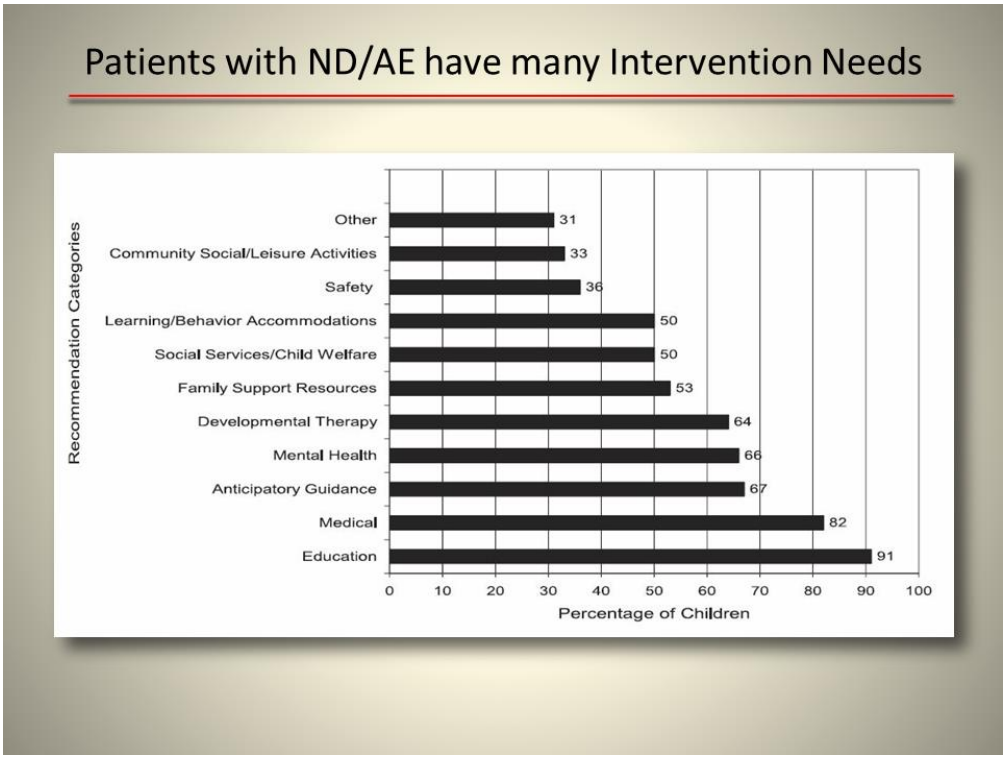


FIG. 24 Among patients evaluated in the WA FASDPN clinics, those with ND/AE received as many intervention recommendations as those with FAS/PFAS and SE/AE.[67]



4C. The term ARND (like Fetal Alcohol Effects (FAE)) should be abandoned and replaced with medically valid terms like SE/AE and ND/AE.

The field continues to struggle with what to label the condition characterized by prenatal alcohol exposure and CNS abnormalities when the FAS facial phenotype is absent.[9] The problem with the diagnostic terms used to date (Fetal Alcohol Effects (FAE)[12] and Alcohol-Related Neurodevelopmental Disorder (ARND)[5]) is they imply that the patient's outcomes are *alcohol effects or alcohol-related.* They imply *alcohol caused the patient's* outcomes. But this presumption in an individual patient is medically invalid because the CNS abnormalities are not specific to (caused only by) prenatal alcohol exposure. There are many other known and unknown risk factors that may be partly or even fully responsible for the patient's outcome. In the absence of the FAS facial phenotype, current medical technology has no ability to confirm or rule-out the causal role of alcohol in an *individual patient*. And it is never just alcohol. There are many other known and unknown risk factors that may be partly or even fully responsible for the patient's outcome.[26] (Figure 21).

The solution to this problem is to replace the term ARND with ND/AE and SE/AE. In 1995, Aase, Jones, & Clarren proposed discontinuation of the term Fetal Alcohol Effects (FAE). "*We propose abandoning the clinical use of the term FAE with its implications of causation. A diagnosis that implies causation should not be applied unless the relationship can be proven. If prenatal alcohol exposure has taken place, but FAS cannot be substantiated, the exposure still should be indicated, and any nonspecific abnormalities or problems noted. Several*

unfortunate consequences may result from inappropriately using the term FAE: Women are stigmatized for having damaged their children by drinking during pregnancy when it is by no means certain that they have done so."[21] But, in 1996, the term Alcohol Related Neurodevelopmental Disorder (ARND) was introduced with all the same limitations of FAE.[5] In 1997, the 4-Digit Code introduced the following terms to replace ARND[1] ND/AE Neurobehavioral Disorder / Alcohol Exposed and SE/AE Static Encephalopathy / Alcohol Exposed One need not confirm a causal link between a patient's alcohol exposure and neurobehavioral disorder to provide effective intervention [26,27,63,67,68] and prevention.[24,38] Access to services should be based on a person's disability, not on what caused their disability.[9,21] Most recently, the DSM-5[69] included this FASD diagnostic subgroup under conditions for further study and chose to label it Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure (ND-PAE). And the recently published recommendations for the Australian FASD diagnostic guidelines chose to label this group Neurodevelopmental Disorder-Alcohol Exposed (ND-AE).[70]

When one uses a term like ARND, one finds themself wanting/needing to require an excessive exposure to alcohol to increase the odds that the child's impairments might in fact be caused, at least in part, by their alcohol exposure. This is a dangerous road to go down. 1) Setting a threshold of excessive exposure for Alcohol-Related Neurodevelopmental Disorder (ARND) does not confirm the patient's alcohol exposure is related to their neurodevelopmental disorder. 2) Alcohol is never the only risk contributing to the neurodevelopmental disorder (Figure 21). 3) One is sending a dangerous message that lower levels of alcohol exposure are safe. 4) And one is blaming a woman for harming her child, when they have no ability to make/defend such a claim. These claims have medical, ethical and even legal consequences.

The WA FASDPN has effectively case-defined, diagnosed, and referred children with "ARND" for intervention services using the 4-Digit Code for 20 years, without calling it ARND. Of the 2, 550 patients with FASD diagnosed in the first 20 years.[26]

- 1,122 were diagnosed with ND/AE (moderate "ARND)
- 612 were diagnosed with SE/AE (severe "ARND)
- 100% have confirmed alcohol exposure, most with exposures as high as those with FAS (Figure 22).
- All risk factors are documented and reported in the medical record, not just the alcohol exposure (Figures 25, 26).
- All receive comprehensive intervention recommendations (Figure 24).[67]
- It is a child's disability, not their exposure that qualifies them for services.
- 84% of families report the intervention services met all or most of their needs. (Figure 31)

The term ARND is not needed to qualify a patient for services. There tends to be a strong belief among some families and clinicians that the only diagnosis that will qualify a child for services is FAS. Along the same lines, it is also believed that the outcome must be blamed on (linked to) the alcohol (e.g., ARND) for a child to qualify for services. Twenty years of family surveys in the WA State FASD clinics confirm that a diagnosis of FAS or ARND is not required to access and benefit from services. Families whose children received a diagnosis of SE/AE or ND/AE were as likely to access and benefit from services as families whose children received a diagnosis of FAS or PFAS.[26] (Figure 31)

FIG. 25 The 4-Digit Code provides generic descriptions of all FASD diagnostic subgroups, including the text above for SE/AE.[3] It is a standard of practice with the 4-Digit Code to clearly state that alcohol is not the only risk factor that could be contributing to a patient's outcomes.

Medical Summary

Final Diagnosis: Static encephalopathy / Alcohol exposed

Fetal Alcohol Syndrome (FAS) is defined by evidence of growth deficiency, a specific set of subtle facial anomalies, and evidence of central nervous system (CNS) damage/dysfunction occurring in patients exposed to alcohol during gestation. Not all individuals exposed to alcohol during gestation have FAS.

In this patient's case, no growth deficiency or characteristic set of facial features were found so the patient does not have FAS, but there was evidence of significant CNS damage/dysfunction as you will see noted on the attached pages. There was also a clear history of exposure to significant amounts of alcohol during gestation. In this situation, we use the term "static encephalopathy" to describe the patient's condition. On the attached sheets are the specific findings in this patient's case that led us to this conclusion. The diagnosis of static encephalopathy does not mean that alcohol is the only cause of the problem. A number of other factors could be contributing to the present issues such as the patient's genetic background, other potential exposures or problems during pregnancy, and various experiences since birth. These kinds of differences may partly explain why there is so much variability in the kinds of specific difficulties that patients with static encephalopathy face.

Individuals with significant CNS abnormalities have structural, neurological, and/or cognitive/behavioral evidence of CNS damage/dysfunction, and should be viewed as individuals with disabilities. The diagnosis of static encephalopathy has implications for educational planning, societal expectations, and health. On the attached sheet you will find a list of specific problems that have been identified that need attention.

5. The 4-Digit Code's method of documenting prenatal alcohol exposure not only detects significant correlations between exposure and outcomes, but also detects exposure patterns that distinguish the diagnostic subgroups.

5A. The 4-Digit Code form used to document prenatal alcohol exposure is both effective and sensitive.

The 1-page standardized form (Figure 26) used to record prenatal alcohol exposure effectively addresses the challenges inherent in obtaining these exposure histories.[3] Full, accurate exposure information is rarely available in a FASD diagnostic clinical setting (Figure 29). Nevertheless, significant correlations are detected between prenatal alcohol exposure and measures of growth deficiency, facial phenotype, and CNS structural and functional abnormalities.[26] For example, frontal lobe volume was found to decrease significantly with increasing number of drinks per drinking occasion and duration of exposure during pregnancy.[16] (Figure 27A). Even patterns that significantly distinguish FAS/PFAS from SE/AE are detected.[9,26] (Figure 27B). And when measures of prenatal alcohol exposure among the 2,550 patients evaluated at the FASDPN clinics over the past year are assessed, the prevalence of drinking all three trimesters declines significantly when plotted across the patients' 30 birth cohorts dating back to 1980 (Figure 27C). As noted above, when the gestalt method of diagnosis[13] was practiced in the FASDPN in the early 1990's, no correlations between alcohol and patient outcomes were detected.[4]

FIG. 26 The 4-Digit Code provides a 1-page standardized form (page 8 of the Diagnostic Form) to record prenatal alcohol exposure that effectively addresses the challenges inherent in obtaining these exposure histories.[3]

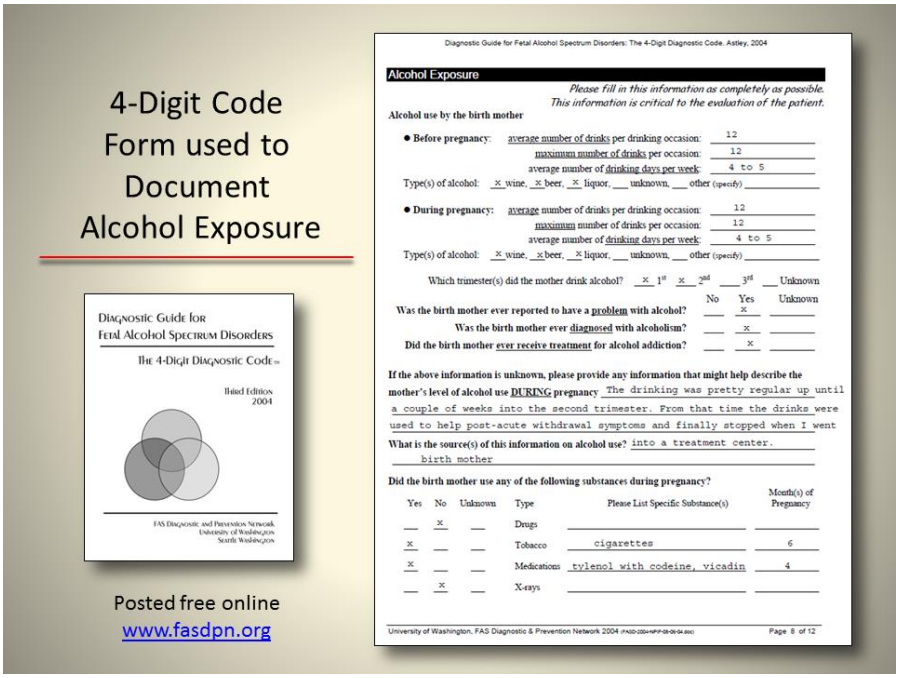
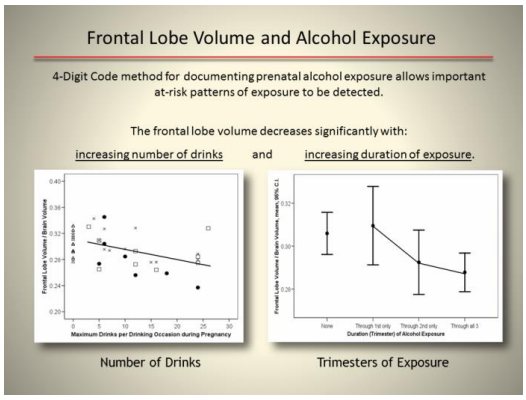


FIG. 27 The 4-Digit Code's method of documenting prenatal alcohol exposure: (A) not only detects statistically significant correlations between exposure and outcomes[16], but also (B) detects statistically significant exposure patterns that distinguish the diagnostic subgroups[26], and (C) detects significant declines in exposure over time.



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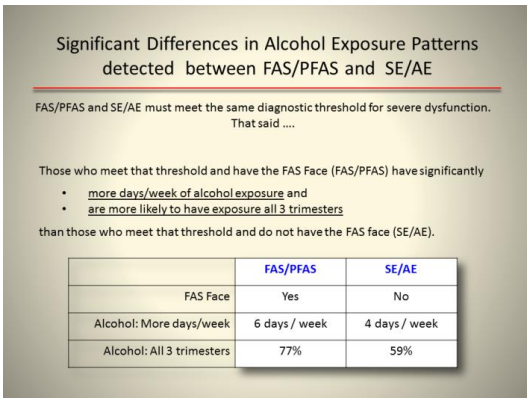

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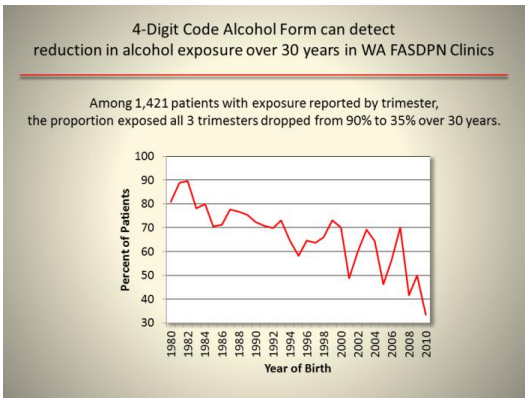
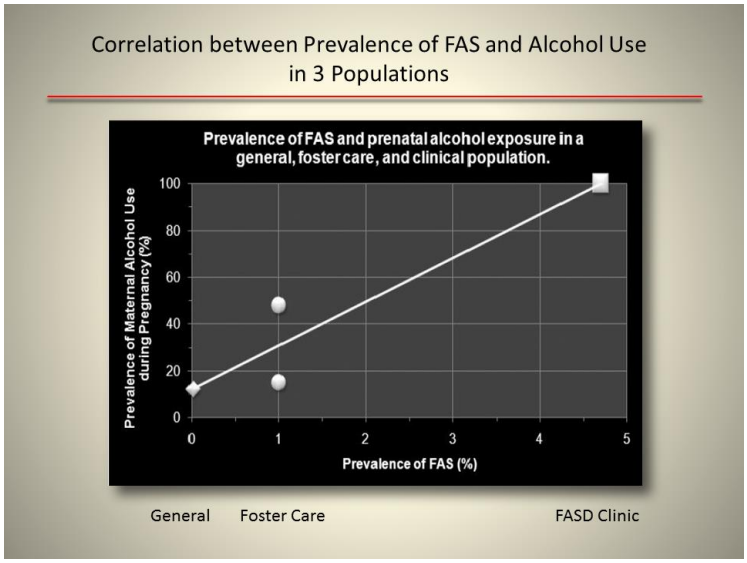


C

5B. The prevalence of maternal alcohol use during pregnancy correlates with the prevalence of FAS as defined by the 4-Digit Code

Two studies document a significant correlation between the prevalence of maternal alcohol use during pregnancy and prevalence of FAS as defined by the 4-Digit Code. In a 10-year active case-ascertainment FAS screening program of foster care in Seattle, WA, the prevalence of maternal drinking during pregnancy in Washington State measured through PRAMS declined significantly (p <0.001) from 1993 to 1998 as did the prevalence of fetal alcohol syndrome among foster children born across those same years (P <0.03) (Figure 6).[24] In a second study, the correlation between the prevalence of FAS to the prevalence of prenatal alcohol exposure across three population bases (the FASDPN clinic, a Seattle foster care program, and the general U.S. population), a significant linear trend was revealed (Figure 28).[26]

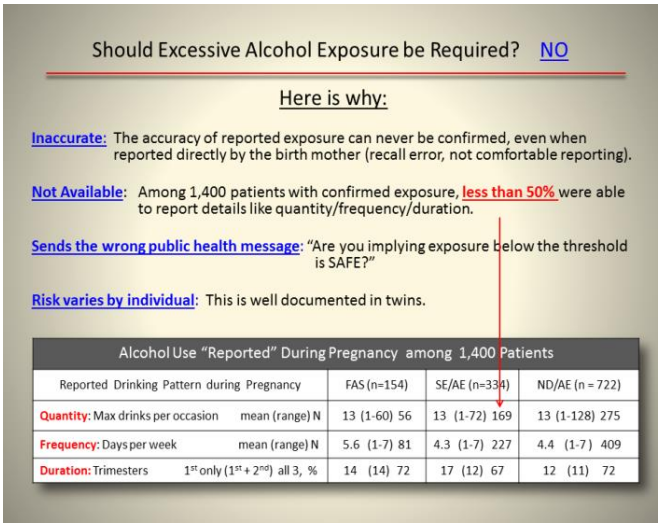
FIG. 28 Prevalence of FAS and prevalence of maternal alcohol use during pregnancy in three populations.[26] ◆General U.S. population (FAS = 0.2%[70], alcohol use = 12.2%). ●King County WA foster care population (FAS = 1%, alcohol use = 15% to 48%).[24] ■ WA FASDPN clinical population (FAS = 4.7%, alcohol use = 100%).[26] Best fit linear trend line: y = 18.989x + 12.352; R-squared = 0.89.



5C. An 'excessive' alcohol exposure history should not be required for a diagnosis the umbrella of FASD.

There remains no clear scientific consensus on what quantity, frequency, and duration of exposure is toxic to the fetus. There are a multitude of reasons for this.[9] 1.) As our tools for measuring outcome become more sensitive, our ability to identify adverse outcomes at lower exposures increases.[72] 2.) Risk from alcohol exposure varies between fetuses[73], even between fraternal twins with ostensibly identical exposure.[74,75] It is not uncommon for one fraternal twin to have full FAS, while the other appears unaffected. Identical twins are typically identically affected. 3.) From a public health perspective, requiring excessive exposure implies lower levels of exposure are 'safe'. Safe for who? 4.) From a research perspective, artificially linking outcome to a threshold level of high exposure prevents assessing the true relationship between exposure and outcome. 5.) From a clinical perspective, if an "excessive" exposure is required, it would be difficult to rationalize why an individual with all the features of FAS would receive a diagnosis of FAS if their exposure was unknown, but would fail to receive a diagnosis of FAS if their exposure was confirmed, but reportedly not excessive. This implies that practitioners have the ability to confirm the accuracy of exposure histories. They do not. Even a birth mother can have difficulty accurately recalling her alcohol use during a pregnancy, especially if that pregnancy was years ago. Among the first 1,400 patients with a confirmed prenatal alcohol exposure evaluated in the WA FASDPN clinics, less than half had measures of quantity, frequency, and duration of alcohol exposure available.[26] This information would be required if an excessive exposure history had to be confirmed. "Excessive"alcohol exposures should not be required for FASD diagnoses (Figure 29). To minimize incorrectly linking a prenatal alcohol exposure to an outcome in an individual patient, diagnostic guidelines should confirm their definition of the FAS facial phenotype is highly specific to prenatal alcohol exposure, avoid use of terms like ARND that imply causality, and report all risk factors that may be contributing to an individual's outcomes, not just the alcohol.

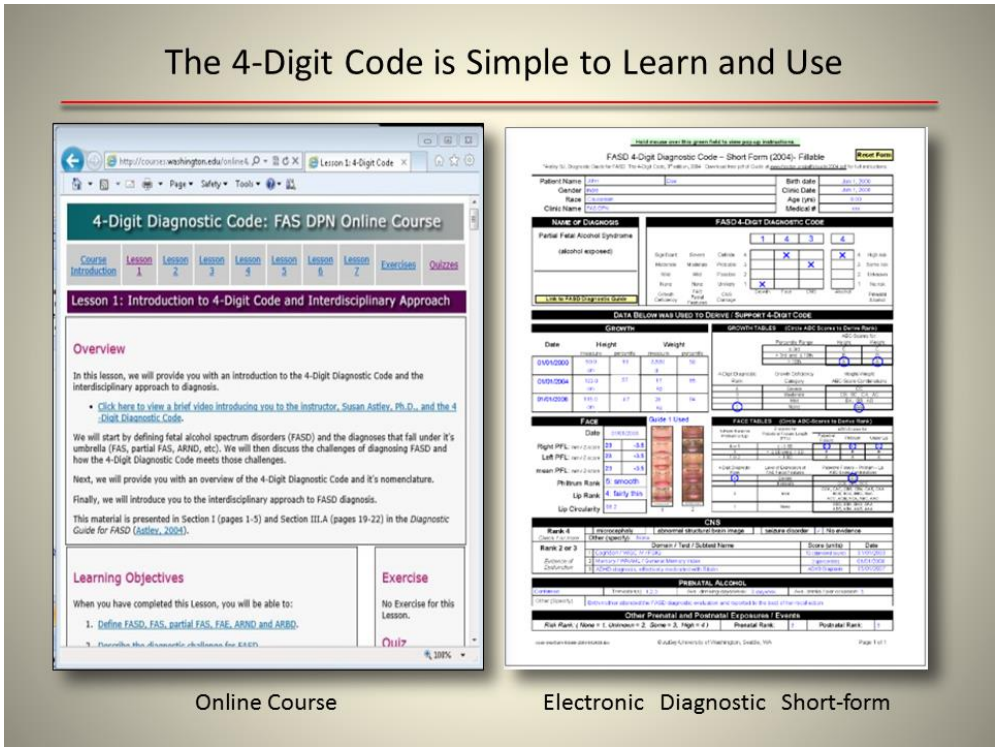
FIG. 29 Four reasons why an FASD diagnostic guidelines should not require 'excessive' prenatal alcohol exposure.[9]



6. The 4-Digit Code has been effectively and efficiently taught to interdisciplinary FASD diagnostic teams worldwide through an inexpensive Online Course.

Clinicians report high satisfaction with the 4-Digit Code. The 4-Digit Code was designed to be a self-taught coding system that could be implemented by simply following the directions provided in the FASD 4-Digit Diagnostic Guide.[1-3] For clinical teams who prefer a more comprehensive introduction to FASD diagnosis and instruction on the use of the 4-Digit Code, the FASD 4-Digit Code Online Course was developed in 2004.[41] (Figure 30A). The Online course is an individual-start, self-paced, fully online program that includes readings, exercises, self-grading quizzes and videos of an entire FASD diagnostic evaluation conducted by the UW FASD interdisciplinary team. Over 700 professionals worldwide have completed the accredited course. Surveys of hundreds of clinicians over 20 years confirm: 93% of professionals describe the 4-Digit Code as clear and 99% of professionals report they would recommend it to others. The 4-Digit Diagnostic Code is practical to use. The Code can be administered using nothing more than the Lip-Philtrum Guides and the 1-page 4-Digit Code Short Form programmed to derive the 4-Digit Code from data entered (Figure 30b) (available free online).

FIG. 30 A. The FASD 4-Digit Code Online Course.[41] B. The 4-Digit Code Short Form is a free pdf posted online that is programmed to generate the 4-Digit Code from data entered into the form.



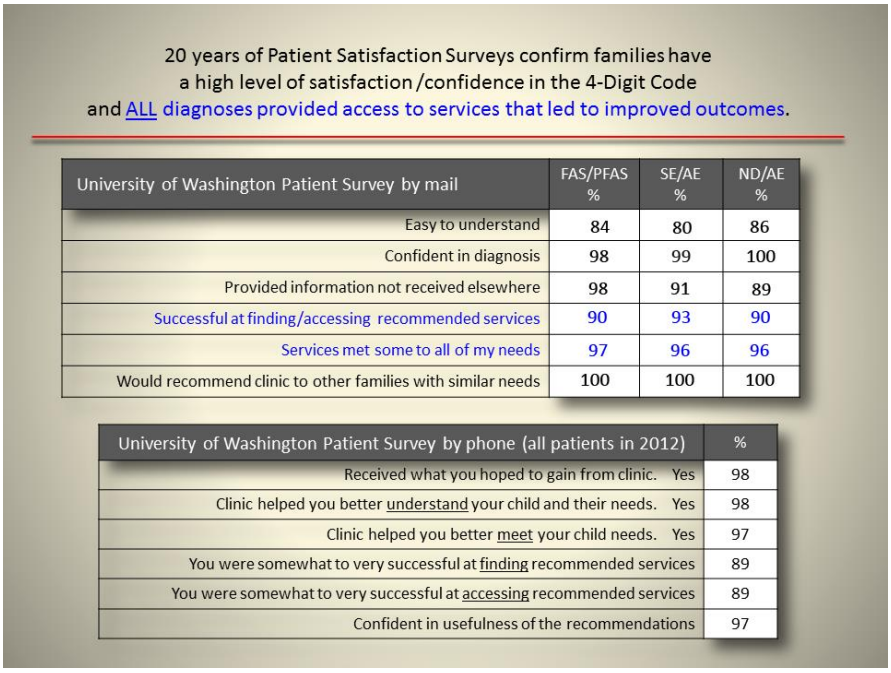
7. The 4-Digit Code has high inter-rater reliability (reproducible) across clinics.

Inter-rater reliability was confirmed to be high prior to the release of the 4-Digit Code, as described above in section 1D, and continued to be high over the next 18 years. Inter-rater reliability between the seven WA FASD Network clinics and the University of Washington Core clinic resulted in an exact match on diagnostic category for 93% of the 677 FASD diagnostic evaluations they conducted over 18 years (Kappa = 0.92, p = 0.000). The most common source of error was facial measurement when the FAS Facial Photographic Analysis software was not used. For example, when clinician's used the six inch plastic ruler to measure the PFL, their measures were on average 1 to 2 mms below the measure derived using the FAS Facial Photographic Analysis Software. This is the direction of error that would be expected due to the slight curvature of the facial plane as demonstrated in an animation on the FASDPN website. A 1-2 mm error can have a significant impact on diagnostic classification accuracy. For example, if a 7 year old girl had PFLs that were truly well within the normal range (25 mm; only 0.4 SDs below the population mean for girls her age[76]), a 1 mm under-estimate (24 mm) would make the PFLs falsely appear to be 1.3 SDs below the mean and thus falsely appear to meet the PFL criteria for the FAS facial phenotype using the CDC or Revised IOM FASD guidelines ($\leq 10^{th}$ percentile or $\geq$ 1.28 SDs below the mean). A 2 mm under-estimate (23 mm) would make the PFLs falsely appear to be 2.1 SDs below the mean and thus falsely appear to meet the PFL criteria for the FAS facial phenotype using the 4-Digit Code ($\leq$ 2 SDs below the mean). Measuring PFLs with a handheld ruler has been confirmed to be highly inaccurate and variable based on data collected over 20 years at the WA FAS DPN. Among eight clinicians measuring PFLs directly with a ruler on 52 to 322 patients each, 12% to 50% of their measurements were 1 or more mm above or below the PFL measured from the child's facial photo using the Facial Software. Six clinicians routinely under-estimated the PFL, two routinely over-estimated the PFL, and one was as likely to overestimate the PFL as underestimate the PFL. The FAS Facial Photographic Analysis Software[33] was developed to overcome these measurement errors and is used by the WA FASDPN as a standard of medical practice for all diagnostic evaluations.

8. Families report high satisfaction and confidence with the interdisciplinary approach to FASD diagnosis using the 4-Digit Code.

Twenty years of patient satisfaction surveys confirm families have a very high level of satisfaction and confidence in the 4-Digit Code administered by an interdisciplinary team.[26] (Figure 31). A 10-question patient satisfaction survey has been sent to all patients evaluated at the UW FASDPN clinic since 1993. The survey may be completed anonymously and comes with a stamped, addressed return envelope to maximize participation in the survey. Patients universally expressed high satisfaction for the FASD diagnostic services provided by the University of Washington (Figure 31). One hundred percent would recommend the Clinic to other families with similar needs. Overall, 92% said they received information they were unable to obtain elsewhere, despite the fact the clinic is located in a large metropolitan area (Seattle) with many genetic, neurodevelopmental, and psychological evaluation services available. Overall, 83% found the explanation of the diagnosis using the 4- Digit Code easy to understand.

FIG. 31 Twenty years of patient satisfaction surveys confirm families have a very high level of satisfaction and confidence in the 4-Digit Code administered by the University of Washington interdisciplinary diagnostic team.[26] Family's whose child received a diagnosis of SE/AE or ND/AE were as likely to report successfully accessing and benefiting from recommended intervention services as family's whose child received a diagnosis of FAS/PFAS.



9. Patient follow-up surveys report all FASD diagnoses (FAS, PFAS, SE/AE, and ND/AE) provided equal access to intervention services that led to improved outcomes.

Perhaps most informative; family's whose child received a diagnosis of SE/AE or ND/AE were as likely to report successfully accessing and benefiting from recommended intervention services as family's whose child received a diagnosis of FAS/PFAS.[26] (Figure 31). This is in contrast to the oft stated belief that a family will not qualify for services if the diagnosis is not FAS/PFAS or at least given a name that implies alcohol is the causal agent (e.g., ARND). Overall, 82.1% of families reported being somewhat to very successful in finding the recommended intervention services and 83.7% reported these services met some to all of their needs.

CONCLUSION

Accurate, reliable, diagnoses across the full continuum of FASD have been available to families and clinicians for over a decade. As medical technology and our understanding of FASD advance, so must our diagnostic methods and tools. It is imperative that advancements in diagnostic methods be guided by an evidence base of rigorously designed, implemented, and peer-reviewed research. When a diagnosis under the umbrella of FASD is made, two individuals are affected directly; the child and the birth mother. The consequences of an incorrect diagnosis for

both mother and child must be considered carefully. Diagnostic guidelines should guide professionals in rendering an accurate diagnosis. A diagnosis reflects the condition of a patient; however, because a diagnosis serves many purposes (e.g., treatment, prevention, communication among specialists, and qualification for services), the process of rendering a diagnosis can sometimes be influenced by those different purposes. The only diagnosis that serves all purposes most effectively is a correct diagnosis. Access to services should be based on an individual's disabilities and not on what caused their disabilities. Services should be available for individuals across the full continuum of FASD, not just those with FAS.

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A TREATMENT IMPROVEMENT PROTOCOL

Addressing Fetal Alcohol Spectrum Disorders (FASD)

TIP 58

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A TREATMENT IMPROVEMENT PROTOCOL

Addressing Fetal Alcohol Spectrum Disorders (FASD)

TIP 58

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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What Is a TIP?

The Treatment Improvement Protocol (TIP) series, which has been published by the Substance Abuse and Mental Health Services Administration (SAMHSA) within the U.S. Department of Health and Human Services (HHS) since 1993, has generally offered best-practices guidelines for the treatment of substance use disorders. For this TIP, the Center for Substance Abuse Prevention (CSAP), a sub-agency within SAMHSA, has drawn on the experience and knowledge of clinical, research, and administrative experts. As behavioral health disorders are increasingly recognized as a major problem, the audience for the TIPs is expanding beyond public and private treatment facilities to include practitioners in mental health, criminal justice, primary care, public health, and other healthcare and social service settings.

The recommendations contained in each TIP are grounded in an evidence base. Evidence includes scientific research findings and the opinion of the TIP consensus panel of experts that a particular practice will produce a specific clinical outcome (measurable change in client status). In making recommendations, the consensus panel engages in a process of "evidence-based thinking" in which they consider scientific research, clinical practice theory, practice principles, and practice guidelines, as well as their own individual clinical experiences. Based on this thinking, they arrive at recommendations for optimal clinical approaches for given clinical situations. Relevant citations (to research outcome reports, theoretic formulations, and practice principles and guidelines) are provided.

TIP Format

This TIP is organized into three parts:

- Part 1 for behavioral health practitioners focuses on providing appropriate counseling methods and frameworks.
- Part 2 for program administrators focuses on providing administrative support to implement adoption of the counseling recommendations made in Part 1.
- Part 3 for clinical supervisors, program administrators, and interested practitioners is an online literature review that provides an in-depth look at relevant published resources. Part 3 will be updated regularly following publication of the TIP.

Ideally, it is envisioned that a supervisor might assemble a small group of counselors, distribute copies of this TIP (which are free), and begin a series of six or so meetings where the materials in the TIP would be reviewed, discussed, and in other ways used as an educational and training vehicle for the improvement of treatment skills (with the particulars of how this training would

be done determined by the individual supervisor, based upon her or his unique situation, needs, and preferences). Thus, after a relatively short period of time and with only limited additional resources, this TIP could help to meet the challenge of fostering a specific kind of improvement in service delivery.

Development Process

The need for this TIP was identified through a collaborative discussion with leadership from each of SAMHSA's three Centers; CSAP, the Center for Substance Abuse Treatment (CSAT), and the Center for Mental Health Services (CMHS). Two consensus panels of experts were convened; one for clinical issues, and the other for administrative guidelines. The TIP was then field reviewed by an external group of subject matter experts, who provided suggestions for further refining the document (see appendix J).

TIPs Online

TIPs can be accessed via the Internet at **http://store.samhsa.gov/home**. The online *Addressing Fetal Alcohol Spectrum Disorders: Part 3, A Review of the Literature*, which will be updated periodically, is available at **http://store.samhsa.gov/home**.

Terminology

Throughout the TIP, the term "behavioral health" is used to refer to both substance abuse treatment and mental health settings. (The term can, in fact, refer to many types of health settings, but the primary audiences for this TIP are substance abuse treatment and mental health providers.) The term "substance abuse" has been used to refer to both substance abuse and substance dependence (as defined by the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* [DSM-5] [American Psychiatric Association 2013]). This term was chosen partly because substance abuse treatment professionals commonly use the term "substance abuse" to describe any excessive use of addictive substances. In this TIP, the term refers to the use of alcohol as well as other substances of abuse. Readers should note the context in which the term occurs in order to determine what possible range of meanings it covers; in most cases, however, the term refers to all varieties of substance use disorders described by the DSM-V.

Foreword

The Treatment Improvement Protocol (TIP) series supports SAMHSA's mission of building resilience and facilitating recovery for people with or at risk for mental or substance use disorders by providing best practices guidance to clinicians, program administrators, and payors to improve the quality and effectiveness of service delivery and, thereby, promote recovery. TIPs are the result of careful consideration of all relevant clinical and health services research findings, demonstrated experience, and implementation requirements. Clinical researchers, clinicians, and program administrators meet to debate and discuss their particular areas of expertise until they reach a consensus on best practices. This panel's work is then reviewed and critiqued by field reviewers.

The talent, dedication, and hard work that TIP panelists and reviewers bring to this highly participatory process have helped bridge the gap between the promise of research and the needs of practicing clinicians and administrators to serve, in the most scientifically sound and effective ways, people who abuse substances. We are grateful to all who have joined with us to contribute to advances in the substance abuse treatment field.

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How This TIP Is Organized

This TIP is divided into three parts:

- *Addressing Fetal Alcohol Spectrum Disorders, Part 1: Background and Clinical Strategies for FASD Prevention and Intervention*
- *Addressing Fetal Alcohol Spectrum Disorders, Part 2: Administrator's Guide to Implementing FASD Prevention and Intervention*
- *Addressing Fetal Alcohol Spectrum Disorders, Part 3: Literature Review*

Parts 1 and 2 are presented in this publication; Part 3 is available only online, at **http://store.samhsa.gov/home**. Each part is described below.

Part 1 of the TIP is for behavioral health providers and consists of three chapters:

- Chapter 1 discusses approaches to preventing FASD; that is, assisting women who are in treatment settings and are pregnant or may become pregnant to remain abstinent from alcohol. In providing these guidelines, this TIP adopts the Institute of Medicine (IOM) model for prevention, which sees prevention as a step along a continuum that also incorpo rates treatment and maintenance.
- Chapter 2 discusses methods for identifying individuals in treatment who have or may have an FASD, referring them for diagnosis where possible, and providing appropriate interventions to meet their needs.
- Chapter 3 provides clinical vignettes designed to realistically portray the provider–client interactions that might take place when providing FASD prevention or interventions.

Part 2 is an implementation guide for program administrators and consists of two chapters.

- Chapter 1 lays out the rationale for the approach taken in chapter 2 and will help readers understand how administrators can provide support for programs and counselors as they address FASD. It is hoped that this knowledge will enhance the ability of treatment programs to address FASD concurrently with other behavioral health needs; addiction, mental health issues, etc.
- Chapter 2 provides detailed information on how to achieve high-quality implementation of the recommendations in ***Part 1***.

Part 3 of this TIP is a literature review on the topic of FASD and is available for use by clinical supervisors, interested counselors, and administrators. *Part 3* includes literature that addresses both clinical and administrative concerns. To facilitate ongoing updates, the literature review will only be available online at **http://store.samhsa.gov/home**.

Preface

Giving Voice to a Hidden Population

- A woman gives birth to a child with a Fetal Alcohol Spectrum Disorder (FASD); no one told her that alcohol consumption during pregnancy could harm the baby.
- A man is repeatedly kicked out of various forms of treatment for noncompliance; he never means to be noncompliant, his special needs and lack of understanding are simply never recognized.
- A teen-aged girl doesn't receive appropriate screening for alcohol use during her pregnancy; her child is removed when she's identified with a substance use disorder, and her child is later found to have an FASD.
- A man repeatedly loses jobs because he can't "follow orders;" he ends up homeless and cycles repeatedly through the social service system.

These stories are not unusual. They are not "worst case scenarios." They are the all-too-common realities of people with an FASD, or women who wanted to have a healthy child but weren't given the basic help they needed before and during pregnancy. And sometimes these realities overlap.

Addressing Fetal Alcohol Spectrum Disorders was written to help you offer hope to these individuals when they present in your setting. This TIP will not ask you to implement a whole new way of treating clients, although you may discover alternative approaches that you want to explore. Rather, it asks you to see people who have or may have an FASD as you see any individual in your care with a significant co-occurring life issue that should be recognized and incorporated into treatment planning. This TIP also asks you to see pregnant women who consume alcohol not through a lens of judgment but as women in need, for whom even a few minutes of information and education can make a lifetime of difference for their health and the health of their babies.

This TIP is also about hope for you as a substance abuse or mental health treatment professional because it gives you another way to view the clients who "just don't get it" or who seem to want to succeed in treatment but can't follow directions, don't make it to appointments, grow restless in group sessions, or generally seem "resistant" with no clear explanation. You can "reframe" your thinking about these clients. Not all of these cases will be explained by FASD, obviously, but making FASD awareness a part of the culture of your agency widens the net of understanding that you can offer to your clients and increases your staff's capabilities for achieving positive outcomes with a higher percentage of them.

Ultimately, SAMHSA's goal is to provide knowledge and assistance to help substance abuse and mental health treatment programs better serve their clients. Providing FASD-informed services is a part of that mission, and is the guiding principle behind the publication of this TIP. Thank you for taking the time to read this publication, and for potentially making a difference for a population that should not remain hidden any longer.

Executive Summary

Introduction

About FASD

Overview

Fetal Alcohol Spectrum Disorders (FASD) is a non-diagnostic umbrella term describing the range of effects that can occur in an individual whose mother consumed alcohol during pregnancy. These effects may include physical, mental, behavioral, and/or learning disabilities with possible lifelong implications. As is discussed in greater detail later in this TIP, these disorders often co-occur with substance abuse and mental health issues, and generally require treatment modifications for successful outcomes. They are 100 percent preventable, however, if those at risk of consuming alcohol during pregnancy are identified and effective prevention strategies are used.

Possible diagnoses within the spectrum include Fetal Alcohol Syndrome (FAS), Partial Fetal Alcohol Syndrome (pFAS), Alcohol-Related Neurodevelopmental Disorder (ARND), Static Encephalopathy/Alcohol-Exposed (SE/AE), and Neurobehavioral Disorder/Alcohol Exposed (ND/AE). (See box, *FASD: Key Terms*, for a fuller description of the disorders within the spectrum and related terminology.)

FASD: Key Terms

- *Fetal Alcohol Spectrum Disorders (FASD)*: Umbrella term referring to a group of disorders caused by prenatal exposure to alcohol; a particular condition on the fetal alcohol spectrum is referred to as "an FASD." Now generally considered to refer to Fetal Alcohol Syndrome (FAS), partial FAS (pFAS), Alcohol-Related Neurodevelopmental Disorders (ARND), Static Encephalopathy/Alcohol-Exposed (SE/AE), and Neurobehavioral Disorder/Alcohol Exposed (ND/AE). See below for all. A variety of diagnostic approaches exist for the disorders within the spectrum; the five most commonly used approaches are included in the key terms below, and are summarized/compared in Appendix E.

Disorders currently or previously described as forms of FASD (in alphabetical order):

- *Alcohol-Related Birth Defects (ARBD)*: Term used to describe individuals who present with congenital defects (including malformations and dysplasia), but not the growth or cognitive/behavioral impairments typically seen in FAS (see definition below). Now less used, although diagnostic guidelines still exist through the Institute of Medicine (IOM; see *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment*, below in this box).
- *Alcohol-Related Neurodevelopmental Disorder (ARND)*: Term created by the IOM to describe individuals with prenatal alcohol exposure and neurodevelopmental abnormalities, but no

FAS facial phenotype. The neurodevelopmental abnormalities are characterized by a complex pattern of behavioral or cognitive conditions inconsistent with developmental level and not explained by genetic background or environment. Problems may include learning disabilities; school performance deficits; inadequate impulse control; social perceptual problems; language dysfunction; abstraction difficulties; mathematics deficiencies; and judgment, memory, and attention problems. The term ARND presents with the same limitations as the discontinued term Fetal Alcohol Effects (see definition below), as one cannot confirm that the neurodevelopmental disorder present in a child with prenatal alcohol exposure was caused by the alcohol exposure in the absence of the FAS facial phenotype. Some diagnostic systems replace the term ARND with Static Encephalopathy/Alcohol-Exposed and Neurobehavioral Disorder/Alcohol Exposed (SE/AE and ND/AE; see definitions below).

- *Fetal Alcohol Effects (FAE)*: Term introduced in the late 1970's to describe less complete partial expressions of FAS (see definition below) in individuals with prenatal alcohol exposure (Clarren & Smith, 1978). Aase, Jones, and Clarren (1995) expressed concern about the validity of the term FAE and proposed abandoning its clinical use, as it implied a causal association (between prenatal alcohol exposure and abnormalities observed in an individual patient) that could not actually be confirmed.
- *Fetal Alcohol Syndrome (FAS)*: Term for what is generally considered to be the most recognizable form of FASD. These individuals exhibit the FAS facial phenotype, impaired growth, and cognitive and behavioral abnormalities.
- *Neurobehavioral Disorder/Alcohol Exposed (ND/AE)*: Term used to describe individuals with prenatal alcohol exposure, moderate cognitive/behavioral impairment (equivalent to moderate ARND), and no FAS facial phenotype.
- *Partial FAS (pFAS)*: Term applied to individuals who exhibit FAS without growth deficiency, or exhibit FAS with most but not all of the facial features.
- *Static Encephalopathy/Alcohol Exposed (SE/AE)*: Term used to describe individuals with prenatal alcohol exposure and severe cognitive/behavioral impairment (equivalent to severe ARND), but no FAS facial phenotype.

Additional terms are presented in alphabetical order:

- *Alcohol-Exposed Pregnancy (AEP)*: Any pregnancy during which the woman drinks any amount of alcohol at any time during the pregnancy. This exposure does not mean the offspring has been affected in any way, but it does place the offspring at some degree of risk for an array of developmental difficulties, including damage to the brain and central nervous system, retardation of growth and other physical effects, and cognitive and behavioral impairments.
- *Diagnosis*: In the context of this TIP, "diagnosis" refers to the formal identification of an FASD by a qualified team and/or dysmorphologist (someone who specializes in structural, or birth, defects). When the TIP discusses the primary diagnosis that brought the client into your substance abuse or mental health setting, or for which your setting is primarily assessing or treating the client, it will be referred to as the "primary treatment issue."
- *Diffuse Brain Damage*: Damage to the brain that is not localized or necessarily the result of a specific traumatic incident to one part of the brain. Such damage can arise from other sources besides alcohol or occur from multiple sources including alcohol. As an AEP (see definition above) can impair the development of multiple parts of the brain of the fetus over the period of pregnancy, an FASD can be considered a manifestation of diffuse brain damage. However, not all diffuse brain damage is the result of alcohol and its expression does not always qualify as an FASD.
- *FASD 4-Digit Diagnostic Code* (Astley, 2004b): Comprehensive, reproducible method for diagnosing the full spectrum of outcomes of patients with prenatal alcohol exposure. First

developed in 1997 by the Washington State FAS Diagnostic and Prevention Network (FAS DPN), the Code was revised in 1999 and again in 2004. Summarized in Appendix E.

- *Fetal Alcohol Spectrum Disorder: Canadian Guidelines for Diagnosis* (Chudley et al., 2005): Canadian guidelines for the diagnosis of FAS, pFAS, and ARND. Summarized in Appendix E.
- *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment* (Stratton, Howe, Battaglia, & the Committee to Study Fetal Alcohol Syndrome, 1996): Diagnosis and treatment guidelines developed by the IOM and published in 1996. These guidelines would be revised by Hoyme, May, and Kalberg (2005) in *A Practical and Clinical Approach to the Diagnosis of Fetal Alcohol Spectrum Disorders: Clarification of the Institute of Medicine Criteria*. Each is summarized in Appendix E.
- *Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis* (Bertrand et al., 2004): FAS diagnosis and referral guidelines developed by the Centers for Disease Control and Prevention (CDC). Summarized in Appendix E.
- *Intervention*: In the context of this TIP, 'intervention' describes 1) a brief methodology for informing women of childbearing age about the results of alcohol screening and the dangers of alcohol use during pregnancy, or 2) the selection of an appropriate treatment methodology to best meet the needs of a client who has or may have an FASD, and any accompanying modifications or accommodations in treatment planning.
- *Screening*: 'Screening' is a familiar term in mental health and substance abuse treatment settings. Validated screening instruments for identifying alcohol use among women are available, and no modification to the basic understanding of screening is necessary for their use. To accomplish the important goal of screening for an individual with an FASD in your setting, formalized tools are limited. However, this TIP does provide indicators to look for, and screening may need to be done more informally through guided observation and/or diagnostic interviewing. In most cases, screening for an FASD will need to occur over time, rather than being a process that can be completed through the use of a simple, brief instrument administered once (e.g., at intake).
- *Static Encephalopathy*: Permanent or unchanging brain damage. Effects on development depend on the part(s) of the brain involved and the severity of the damage.
- *Teratogen*: Any substance that can damage a developing fetus. Common teratogens include alcohol, tobacco, lead, radiation, and exposure to infectious disease.

Prevalence

The prevalence of FAS in the United States has been estimated at 1–3 per 1,000 live births among the general population (Stratton et al., 1996) and 10–15 per 1,000 in some higher-risk populations, such as children residing in foster care (Astley, Stachowiak, Clarren, & Clausen, 2002; Astley, 2004a). The prevalence of the full spectrum of FASD in the general population is estimated at 9.1 per 1,000 live births, though a review of in-school screening and diagnosis studies suggest that the national rate could potentially be closer to 50 per 1,000 (May et al., 2009). In addition, recent retrospective analyses of hospital admissions data indicate that under-reporting of alcohol misuse by women may further disguise true prevalence (Morleo et al., 2011).

Although prenatal alcohol exposure has been clearly established as a causal factor for FASD in animal models, the amount of alcohol required to cause damage to the fetus remains in question, and may differ based on the individual. Factors such as dose of alcohol, pattern and timing of exposure, genetics, whether the mother also smoked and/or used other drugs, general health and nutrition of the mother, her level of stress and/or trauma, and her age all may play a role in the impact that alcohol has on the developing fetus (Guerri, Bazinet, & Riley, 2009). Animal studies do suggest that binge drinking (four or more drinks on one

occasion) is associated with more severe effects (Bonthius & West, 1988; Clarren, Astley, Gunderson, & Spellman, 1992), and it is generally asserted that there is no known 'safe' level of alcohol consumption during pregnancy (Office of the Surgeon General, 2005; Hicks & Tough, 2009; Feldman et al., 2012).

Not every woman who consumes alcohol during pregnancy will give birth to a child with an FASD. However, because science has not determined a safe level of alcohol that may be consumed during pregnancy, the possibility of an FASD is created any time a woman consumes alcohol while pregnant.

Due to the range of deficits—and variability in degree of severity of each deficit—within the diffusely damaged brain, FASD can present as functionally different in each individual that is affected. However, certain cognitive, behavioral, and adaptive functioning problems are common across the spectrum, including lower IQ, impaired learning ability, and difficulty processing information (such as not being able to remember or follow instructions, or poor verbal receptive skills) (Streissguth, Barr, & Bookstein, 1996; Bertrand et al., 2004; Streissguth et al., 2004; Astley et al., 2009a; Astley, 2010). Physical abnormalities and facial dysmorphology (i.e., congenital malformation) are only common with FAS. Other functional issues regularly observed include attention deficit (Nanson & Hiscock, 1990; Lee, Mattson, & Riley, 2004), decreased proficiency in cognitive planning (Kodituwakku, Handmaker, Cutler, Weathersby, & Handmaker, 1995; Kodituwakku, Kalberg, & May, 2001; Rasmussen, 2005), reduced working memory (Burden, Jacobson, Sokol, & Jacobson, 2005; Astley et al., 2009b; Green et al., 2009), reduced response inhibition (Noland et al., 2003; Mattson, Crocker, & Nguyen, 2011), socially inappropriate behaviors (Bishop, Gahagan, & Lord, 2007; Jirikowic, Kartin, & Olson, 2008; Mattson, Crocker, & Nguyen, 2011), and deficits in fine motor (Kalberg et al., 2006; Jirikowic et al., 2008) and visual-spatial functions (Chiodo, Janisse, Delaney-Black, Sokol, & Hannigan, 2009; Mattson et al., 2010).

Cost Factors

Estimates of the cost to raise a child with an FASD vary depending on the source and the factors included in the analysis, and detailed cost estimates are generally only available in relation to the specific condition of FAS. Nonetheless, these costs are significant. In an analysis of medical expenditures for pediatric Medicaid enrollees, Amendah, Grosse, and Bertrand (2010) found that, for a child with identified FAS, incurred health costs were nine times higher than for children without an FASD. Astley, Bailey, Talbot, and Clarren (2000a) further isolated cost factors in a demonstration of primary FAS prevention in an FASD diagnostic clinic that targeted high-risk women; using this approach, the cost of raising a child with FAS was found to be roughly 30 times higher than the cost of preventing FAS in the child.

The most widely acknowledged estimate of the lifetime cost of care for an individual with an FAS is that of Lupton, Burd, and Harwood (2004), who adjusted figures originating with Harwood and Napolitano (1985) for 2002 dollars to suggest that the figure was roughly $2 million (including medical treatment, special education, residential care for persons with mental retardation, and productivity losses; in 2012 dollars, this would be over $2.5 million). The overall annual cost of FAS to the U.S. healthcare system (based on an assumption of 2 cases per 1,000 live births) is estimated at $5 billion (Lupton et al., 2004).

Part 3 of this TIP, the online Literature Review, contains additional information on FASD surveillance and cost factors, as well as the impact of alcohol on the brain and behavior.

Historical Background

FASD is often described as a 'new' or 'recent' discovery. In fact, references to the harmful effects of maternal drinking on infant outcome date back to biblical times: "Behold, thou shalt conceive, and bear a son; and now drink no wine or strong drink" (Judges 13:7, as noted in Clarren & Smith, 1978). In addition, several comprehensive descriptions were compiled by physician groups in the 18th and 19th centuries (Royal College, 1726; Sullivan, 1899; Goodacre & Mercer, 1965). The more recent history commonly referred to begins in 1968, when Lemoine, Harousseau, Borteyni, and Menuet from France published an article describing children with distinctive facial features and other symptoms related to prenatal alcohol exposure. In 1970, unaware of the Lemoine publication, Ulleland and colleagues published similar observations describing a small group of alcohol-exposed infants admitted to several high-risk maternal-child health clinics at the University of Washington (Ulleland, Wennberg, Igo, & Smith, 1970; Ulleland, 1972). This work would eventually lead to a seminal, collaborative article describing the pattern of outcomes associated with prenatal alcohol exposure (Jones, Smith, Ulleland, & Streissguth, 1973), as well as the publication that coined the term FAS (Jones & Smith, 1973).

In the roughly 40 years that have followed, extensive study has been conducted on alcohol's teratogenic effects, as well as on interventions for women of childbearing age who consume alcohol, leading to several significant federal milestones in addressing FASD. In 1996, the Institute of Medicine (IOM) published *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment* (Stratton et al., 1996), leading the National Institute on Alcohol Abuse and Alcoholism (NIAAA) to establish the Interagency Coordinating Committee on FASD (originally Interagency Coordinating Committee on FAS) to address that publication's recommendations. Then, in 2000, Congress set forth mandates related to children's health, including FASD, leading the Centers for Disease Control and Prevention (CDC) to establish the National Task Force on FAS and FAE (completed in 2007), and SAMHSA to establish the FASD Center for Excellence in 2001.

In the decade since the Congressional mandates, the research and knowledge base around FASD has expanded greatly. According to Goodlett (2010), a PubMed search of FAS-, FASD-, or fetal alcohol-specific terminology at the end of 2010 returned nearly 3,900 articles published since 1973, of which more than 38 percent had been published since 2000. This growth is translating to practice: Since 2001, the FASD Center for Excellence alone has funded more than 70 subcontractors across the United States to carry out pilot efforts to implement FASD-related services into existing programs, including substance abuse and mental health treatment settings.

This body of work has revealed an unfortunate paradox: Individuals with an FASD require more intensive and personalized services, and early diagnosis and intervention have been identified as critical to improved outcomes and minimized secondary disabilities (Streissguth et al., 2004; Astley, 2010). Yet, individuals with an FASD often go undiagnosed or are misdiagnosed (Greenbaum, Stevens, Nash, Koren, & Rovet, 2009), are difficult to identify early and may not receive appropriate early intervention (Olson, Jirikowic, Kartin, & Astley, 2007), and often receive services that do not account for their disabilities and thus may result in poor outcomes.

Audience: Who Should Read This TIP?

This TIP is designed for use by behavioral health providers, particularly substance abuse and mental health treatment professionals, not only because these are the primary constituencies of SAMHSA but also because individuals with FASD experience higher rates than the general population of both substance abuse and mental health issues (Streissguth et al., 1996; O'Connor et al., 2002; Streissguth et al., 2004; Clark, Lutke, Minnes, & Quellette-Kuntz, 2004; Astley, 2010). In addition, individuals with an FASD exhibit higher rates of life problems commonly encountered in substance abuse and mental health treatment populations, including higher risk of suicide (Huggins, Grant, O'Malley, & Streissguth, 2008), exposure to multiple traumas throughout the lifespan (Henry, Sloane, & Black-Pond, 2007; Greenbaum et al., 2009), homelessness (Fryer, McGee, Matt, Riley, & Mattson, 2007), and increased interaction with the criminal justice system (Streissguth et al., 1996; Streissguth et al., 2004).

This TIP is also important because there are great opportunities for FASD prevention in mental health and substance abuse treatment settings. According to the 2009 *National Survey on Drug Use and Health* (NSDUH), 17.1 percent of women age 18 or over in the U.S. received mental health treatment or counseling in 2009, compared to only 9.2 of men in the same age group (Center for Behavioral Health Statistics and Quality [CBHSQ], 2010), while the *Treatment Episode Data Set* (TEDS) indicates that 33.0 percent of admissions to substance abuse treatment facilities in 2011 were female, more than half of whom (50.5 percent) indicated alcohol as a primary, secondary, or tertiary substance of abuse (CBHSQ, 2013). Thus, these settings provide ideal opportunities to implement brief, effective approaches to preventing an AEP.

Part 1 of this TIP is for frontline personnel and consists of three chapters:

- *Chapter 1* discusses approaches to FASD prevention; that is, assisting women who are in treatment settings and are pregnant or may become pregnant to remain abstinent from alcohol. In providing these guidelines, this TIP adopts the IOM model for prevention, which sees prevention as a step along a continuum that also incorporates treatment and maintenance.
- *Chapter 2* discusses methods for identifying individuals in treatment who have or may have an FASD, referring them for diagnosis where possible, and providing appropriate interventions to meet their needs. These clients are assumed to be adolescent or older, as they would need to be capable of presenting in treatment on their own (although the TIP strongly recommends including the family in treatment, when possible).
- *Chapter 3* provides clinical vignettes designed to realistically portray the provider–client interactions that might take place when providing FASD prevention or interventions.

Part 2 provides administrators with strategies and tools for undertaking the activities that will support treatment professionals and clients and for making the changes required to incorporate FASD prevention and/or intervention in daily practice. Part 2 also includes methods, materials, resources, and examples to assist administrators with quality improvement and ongoing evaluation of the necessary programmatic changes.

At the same time, the clinical and administrative guidance set forth in this TIP has strong applicability across healthcare and social service settings. While the client interactions

described generally involve substance abuse and mental health treatment, any provider assisting women at risk of an AEP or assisting individuals who may have an FASD can implement the majority of these recommendations if they adapt them for that professional's setting. This is particularly the case if the setting in question overlaps with the life issues that more frequently occur among individuals with an FASD, as discussed above (i.e., criminal justice, housing, primary care).

Barriers to Treatment: The Need for the TIP

For a variety of reasons, including the somewhat hidden nature of many of the symptoms, individuals with an FASD are frequently misdiagnosed or their condition is not recognized (Olson et al., 2007; Greenbaum et al., 2009). This, in turn, leads to care that is not matched to the patient's needs and strengths, increasing the risk for secondary disabilities (Streissguth et al., 2004).

Added to this, recent statistics on drinking among pregnant women show that AEP prevention is as serious an issue as appropriate services for individuals who have an FASD (see box, *Drinking Rates Among Pregnant Women*, in the next chapter). AEP prevention may not be a familiar goal in mental health and substance abuse treatment settings. Yet these are ideal settings in which to prevent prenatal alcohol exposure, as behavioral health professionals routinely work with women of childbearing age (age 10–49 years). Treatment can then have a positive affect not only on the client, but on his or her family and generations to come.

Ideally, this TIP will help to alleviate many barriers to providing successful treatment for these two populations, including:

- The application of treatment approaches that, while effective with general populations, may not be ideally suited to the needs of individuals with an FASD;
- A lack of awareness among treatment professionals of the rapid developments in the field of FASD services over the last decade; and
- Helping clients deal with feelings of shame, loss, or fear of discrimination.

Lack of Success With Typical Treatment Approaches

Prenatal exposure to alcohol has many teratogenic effects, among them that it can alter brain structure and function, meaning that people with an FASD do not process information in the same ways that those without an FASD do. These effects are permanent; an FASD cannot be 'cured.' Processing differences that may affect treatment can take many forms, including:

- Poor receptive language skills (difficulty with complex language and multiple instructions);
- Difficulty with social cognition and accurately understanding social cues;
- Difficulty taking in new information, and in generalizing learning to new settings; and
- Not always connecting cause and effect (particularly if the effect is delayed).

Expert consensus suggests that treatment approaches that rely on an assumption of 'normal' functioning of these cognitive processes are likely to be less effective with individuals with an FASD. This appears to be true for both mental health and substance abuse treatment settings.

Cognitive–Behavioral Therapy (CBT) models, for instance, are verbally based insight therapies designed to reduce target symptoms, and are based on the idea that inaccurate thoughts are linked to maladaptive feelings and behaviors. However, CBT approaches do not fit well

given that individuals with an FASD have biologically based cognitive deficits (O'Connor et al., 2002). Behaviors of individuals with an FASD may result from errors in thinking that are difficult to change because of underlying diffuse brain damage. Modification to CBT, and adding other approaches, will be needed to maximize treatment efficiency and success.

The disease model of substance abuse treatment, which advocates lifelong abstinence from alcohol, also relies on the assumption that a client has normative function. Behavioral health professionals assume that the client can comprehend that he or she has a 'disease' and also that he or she can plan ahead to recognize why it is important to achieve abstinence. For an individual with an FASD, this link may be difficult to make, and so his or her substance abuse or mental health target symptoms may be harder to change (and change harder to maintain) because of the underlying diffuse brain damage.

Rapid Developments in the Field

The tremendous growth in FASD-related research and the establishment of the SAMHSA FASD Center for Excellence have practical implications for behavioral health professionals, in that the field of FASD-related practices is growing dynamically. Much of the practical guidance in this TIP has emerged only over the last 5 to 10 years. Even professionals who have had some form of FASD training in the past are likely to discover new and useful strategies in this TIP that can be effectively applied in their programs.

Treatment Barriers

Despite their unique treatment needs, clients with an FASD or pregnant women at risk of an AEP still share with any other client a significant, common barrier to treatment success: The impact of negative self-perception. An individual with an FASD or a woman who has consumed alcohol during pregnancy may perceive themselves negatively, either because of internal feelings of shame, a sense of not belonging, or due to experiencing external shaming or judgment. These internal feelings and external experiences can each become a barrier to treatment (Astley, Bailey, Talbot, & Clarren, 2000b; Salmon, 2008).

When implementing the practices recommended in this TIP, behavioral health professionals are urged to keep sight of the importance of addressing the client's feelings and experiences, as well as the need for sensitivity to issues such as gender, ethnicity, cultural background, and sexuality, as these factors impact treatment success among individuals with an FASD and women of childbearing age as significantly as any other treatment population.

"We must move from viewing the individual as failing if s/he does not do well in a program to viewing the program as not providing what the individual needs in order to succeed."

Dubovsky, 2000

1 Prevention of Alcohol-Exposed Pregnancies Among Women of Childbearing Age

IN THIS CHAPTER

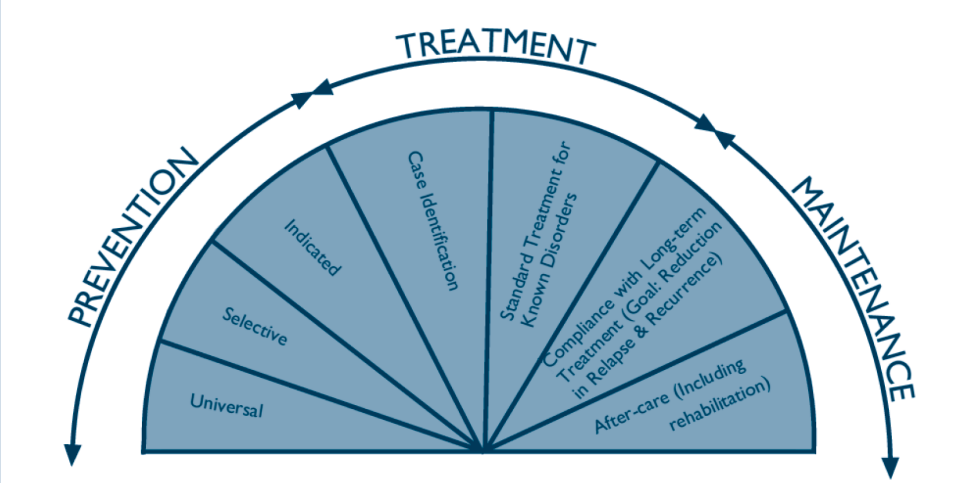
Introduction

One act of AEP prevention can positively impact the life of the mother and the life of the unborn child. One change in how services are provided can multiply that impact many times over.

This TIP adopts the IOM continuum of care model, which sees prevention as a step along a continuum that also incorporates treatment and maintenance (see Figure 1.1, below). The IOM model defines three types of prevention: universal, selective, and indicated.

- *Universal prevention* "[a]ddresses [the] general public or [a] segment of [the] entire population with average probability, risk or condition of developing [a] disorder" (Springer & Phillips, 2007). Universal prevention can take a variety of forms, including media campaigns, large-scale health initiatives (e.g., immunization), point-of purchase signage, and warning labels on products.
- *Selective prevention* is designed for a "[s]pecific sub-population with risk significantly above average, either imminently or over [his or her] lifetime" (Springer & Phillips, 2007), and can include "screening women for alcohol use, training healthcare professionals, working with family members of pregnant women who abuse alcohol, developing biomarkers, brief interventions, and referrals" (Grant, 2011).
- *Indicated prevention* "[a]ddresses identified individuals with minimal but detectable signs or symptoms suggesting a disorder" (Springer & Phillips, 2007), such as pregnant women who drink heavily, or women who have already given birth to a

Figure 1.1: The IOM Continuum of Care Model



Source: Springer & Phillips, 2006; 2007.

child with FASD and continue to drink. Indicated prevention can include some of the same methods applied in selective prevention, but applied more intensively based on the severity of the alcohol-related problem.

For the purposes of the AEP prevention discussion in this chapter, women of childbearing age (i.e., females age 10–49) in your treatment setting should receive AEP prevention based on the following:

- *Universal prevention*: A woman who is not pregnant, and either reports no alcohol use or does not screen positive for at-risk alcohol use;
- *Selective prevention*: A woman of childbearing age who reports alcohol use but has only one of the two indicators for an indicated intervention; she is either pregnant but does not screen positive for at-risk alcohol use, or she screens positive for at-risk alcohol use but is not pregnant; or
- *Indicated prevention*: A woman of childbearing age who screens positive for at-risk alcohol use and is pregnant.

This chapter will first discuss screening, then appropriate brief interventions for AEP prevention in each of the three categories, before discussing treatment issues and referral. In each category, screening is a vital starting point before moving on to appropriate prevention, treatment, or referral.

Professional Responsibility to Screen

As the box "Risk Factors for an AEP" (next page) makes clear, a variety of factors can impact a woman's consumption of alcohol during pregnancy. These and other factors make it critical to inquire about alcohol use among *all* women of childbearing age in behavioral health settings for alcohol consumption:

- There is *no* known safe level of alcohol consumption during pregnancy, and even low levels of prenatal alcohol exposure have been shown to negatively impact a fetus (Chang, 2001).

- Screening facilitates the implementation of appropriate interventions, at the earliest possible point (Leonardson, Loudenburg, & Struck, 2007).
- Prevented AEP can result in significant cost savings through prevented cases of FASD and reduced use of the health and social services systems (Abel & Sokol, 1991; Astley et al., 2000a; Lupton et al., 2004; Astley, 2004a).
- Screening is an ethical obligation, one that should be conducted equally of men and women regardless of race and economic status, and which should be performed with women using instruments that are designed for women (Committee on Ethics of the American College of Obstetricians and Gynecologists [ACOG], 2008). Additionally, in an FASD prevention study assessing the feasibility of identifying high-risk women through the FASD diagnostic evaluation of their children, Astley and colleagues (2000a) concluded that these women are not only at high risk for producing more children damaged by alcohol exposure, but they themselves often face serious adverse social, mental, and physical health issues, as well. Thus, one could argue that it would be unethical to ignore their existence and ignore opportunities to provide them with advocacy support and primary prevention intervention.
- Awareness *does* create change: Statistics from SAMHSA's NSDUH (May 21, 2009) suggest that drinking rates among women drop considerably during pregnancy, particularly in the second and third trimesters when there is a much higher awareness of pregnancy status.

In addition, screening:

- Gives the client permission to talk about drinking;
- Helps to identify and or clarify co-occurring issues;
- Minimizes surprises in the treatment process; and
- Can mean more effective treatment.

Risk Factors for an AEP

Substance Abuse/Mental Health Factors

- *History of alcohol consumption (NIAAA, 2000; Bobo, Klepinger, & Dong, 2007)*
- *Family background of alcohol use (Stratton et al., 1996; Leonardson et al., 2007)*
- *History of inpatient treatment for drugs or alcohol and/or history of inpatient mental health treatment (Project CHOICES Research Group, 2002)*

Personal/Sexual/Family Factors

- *Previous birth to a child with an FASD (Kvigne et al., 2003; Leonardson et al., 2007)*
- *Lack of contraception use/unplanned pregnancy (Astley et al., 2000b)*
- *Physical/emotional/sexual abuse (Astley et al., 2000b)*
- *Partner substance use/abuse (Stratton et al., 1996; Leonardson et al., 2007)*
- *Multiple sex partners (Project CHOICES Research Group, 2002)*
- *Smoking (CDC, 2002; Leonardson et al., 2007)*
- *Never having been tested for HIV (Anderson, Ebrahim, Floyd, & Atrash, 2006)*
- *Lack of education, income, and/or access to care (Astley et al., 2000a)*

Drinking Rates Among Pregnant Women

According to SAMHSA's 2010 NSDUH, "Among pregnant women aged 15 to 44, an estimated 10.8 percent reported current alcohol use, 3.7 percent reported binge drinking, and 1.0 percent reported heavy drinking. These rates were significantly lower than the rates for non-pregnant women in the same age group (54.7, 24.6, and 5.4 percent, respectively). Binge drinking during the first trimester of pregnancy was reported by 10.1 percent of pregnant women aged 15 to 44" (Office of Applied Studies [OAS], 2011). All of these estimates are based on data averaged over 2009 and 2010. (Binge drinking for women has been defined by NIAAA as four or more drinks on one occasion [2004]).

In telephone interviews with 4,088 randomly selected control mothers from the CDC's National Birth Defects Prevention Study who delivered live born infants without birth defects during 1997–2002, Ethen and colleagues (2009) found even higher numbers: 30.3 percent of respondents reported alcohol use during pregnancy, with 8.3 percent reporting binge drinking during pregnancy (approximately 97 percent of those indicating binge drinking stating that it was during the first trimester).

In addition, one study of stool and hair samples of neonates who had been prenatally exposed to heavy ethanol use suggested that these children were also 3.3 times more likely to have been exposed to amphetamines and twice as likely to have been exposed to opiates, both of which can also impair long-term child development (Shor, Nulman, Kulaga, & Koren, 2010). Another recent study found that, among 1,400 patients with prenatal alcohol exposure attending an FASD diagnostic clinic in Washington state, 62 percent were prenatally exposed to tobacco, 37 percent were prenatally exposed to marijuana, and 38 percent were prenatally exposed to crack cocaine (Astley, 2010).

Statistics from SAMHSA's TEDS and from SAMHSA's NSDUH indicate a potentially greater need to address the FASD issue specifically in substance abuse treatment settings: More than 22 percent of pregnant women admitted into treatment from 1992 to 2006 indicated alcohol as their primary substance of abuse (OAS, 2006).

Lastly, 49 percent of all pregnancies in the United States are unintended (Finer & Henshaw, 2006). As a result, many women will consume alcohol without knowing that they are pregnant.

Procedures for Screening

Behavioral health settings are busy, and screening procedures must be efficient. Figure 1.2, *Screening Decision Tree for AEP Prevention*, provides a procedure for an opening question about alcohol use, moving on to screening (if necessary), suggested instruments for screening, and next steps. The goal of screening is to determine, as quickly and as accurately as possible, whether a client is at risk and therefore brief intervention and treatment or referral is warranted.

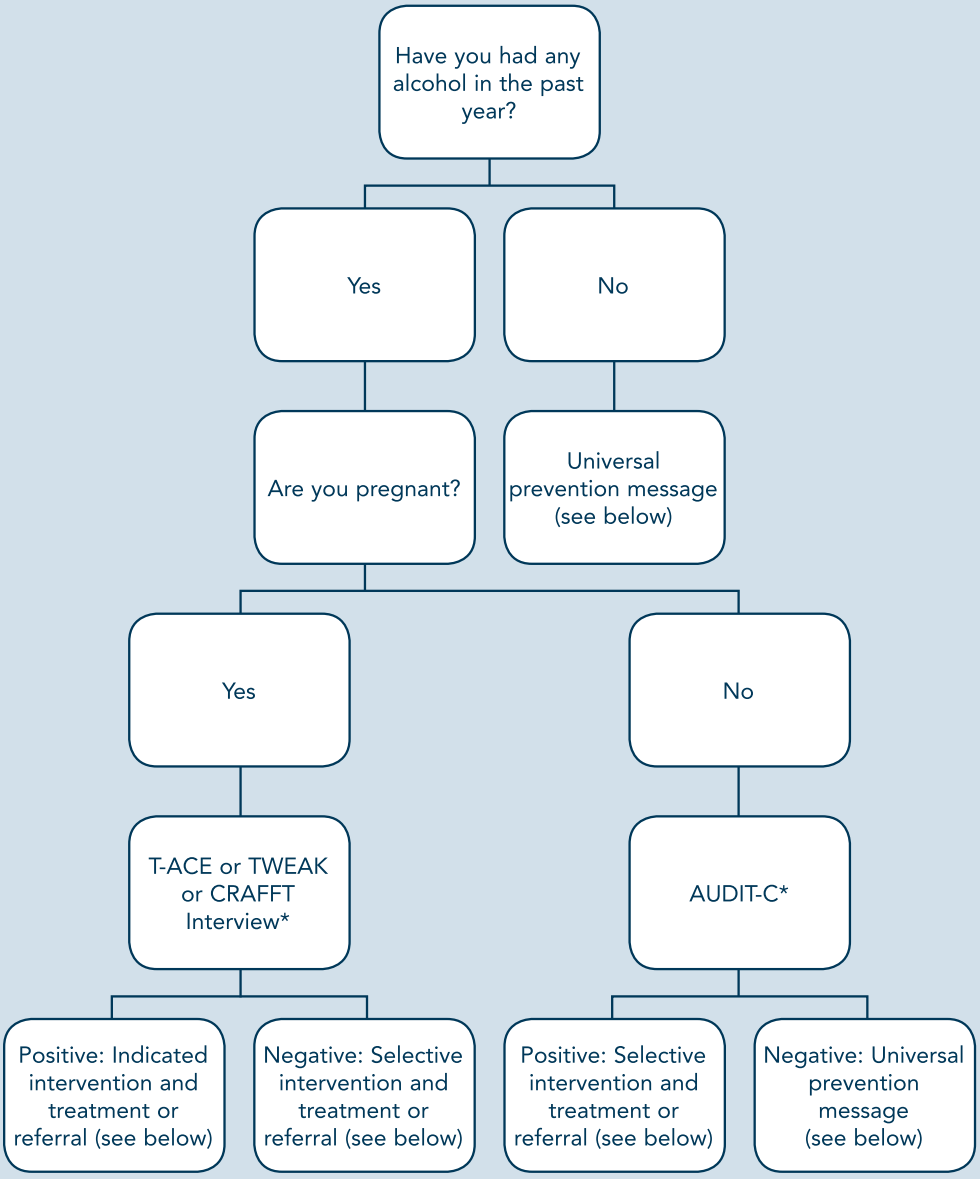
The screening instruments recommended in Figure 1.2 are not the only options available for determining client alcohol use, but are validated as indicated in the decision tree (Sokol & Clarren, 1989; Russell, 1994; Chang, 2001). Nonetheless, if your agency does not use these instruments or does not have a 'perfect' alternative, it is better to screen with what is available to your program than to not screen women of childbearing age at all.

Part 3 of this TIP, the online Literature Review, includes further discussion of these and other alcohol screening instruments for use with women.

Screening should be done with sensitivity to the client's level of health literacy, or, "the degree to which people have the capacity to

Figure 1.2: A Screening Decision Tree for AEP Prevention

AEP prevention can be simple and brief. The TIP consensus panel developed the following Screening Decision Tree for AEP Prevention to help behavioral health providers quickly touch upon the topic of alcohol use with all women of childbearing age, and then provide brief but effective prevention or intervention.



* The T-ACE and TWEAK are validated for use with pregnant women. The CRAFFT Interview may be more helpful when assisting adolescent clients. The AUDIT-C is validated for use with non-pregnant women. All of these instruments are reprinted in Appendix B of this TIP.

obtain, process, and understand basic health information and services needed to make appropriate health decisions" (Parker, Ratzan, & Lurie, 2003; Liechty, 2011). More than a third of adults in the United States do not have adequate health literacy (Kutner, 2006; Liechty, 2011), so the prevention message may need to be simplified and reinforced by asking the client on several occasions and in a variety of ways. This means that your agency will likely need to screen at several different points in time.

In addition, talking about alcohol use or seeking help for an alcohol-related problem can be potentially embarrassing or difficult for the client (NIAAA, 2005). Counselors should be conscious of this risk, and be respectful when raising the issue of alcohol use. Additional sources of information that can help to identify alcohol use include collateral reports from family and friends of the client, and client medical/court records.

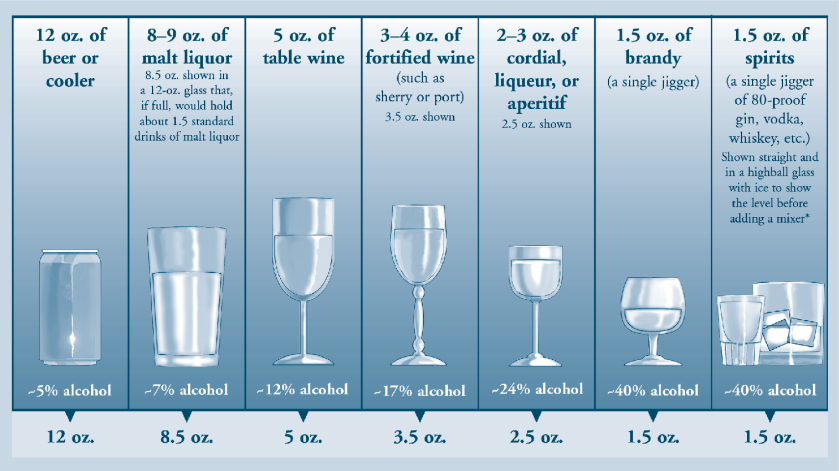
Vignette #2 in Part 1, Chapter 3 incorporates discussion of drink size and the use of a visual aid with a client.

Selecting an Appropriate Prevention Approach

Based on the results of your client screening, the next step is to decide on an appropriate brief approach: Universal prevention message or selective or indicated brief intervention. Brief interventions are associated with sustained reduction in alcohol consumption by women of childbearing age, and those discussed have shown promise for being adaptable to various settings and needs (Fleming, Barry, Manwell, Johnson, & London, 1997; Manwell, Fleming, Mundt, Stauffacher, & Barry, 2000; Burke, Arkowitz, & Menchola,

What Is a Standard Drink?

All clients being screened for alcohol consumption should be given a clear indication of what constitutes a 'standard drink.' A standard drink in the United States is any drink that contains about 14 grams of pure alcohol (about 0.6 fluid ounces or 1.2 tablespoons). Below are U.S. standard drink equivalents. These are approximate, since different brands and types of beverages vary in their actual alcohol content.



Source: *Helping Patients Who Drink Too Much: A Clinicians Guide* (Updated 2005 Edition), NIAAA, p. 24. NIH Publication No. 07-3769.

2003; Project CHOICES Intervention Research Group, 2003; Chang et al., 2005; Grant, Ernst, Streissguth, & Stark, 2005; O'Connor & Whaley, 2007).

When using these prevention approaches, counselors should remember that no intervention constitutes full treatment of a woman's alcohol use. Each is designed simply to encourage a dialogue about alcohol and begin a process of change. Each should be the basis for ongoing evaluation and an informed approach to treatment or referral. For programs that do not have existing approaches to substance abuse treatment, procedures for appropriate referral are discussed after the brief interventions.

Universal Prevention

As indicated in Figure 1.2, *Screening Decision Tree for AEP Prevention*, a woman who is not pregnant, and either reports no alcohol use or does not screen positive for at-risk alcohol use, can receive a simple universal prevention message. Consider the following scripted messages.

Universal AEP Prevention Statement and Possible Follow-Up Questions

"It's great that you're choosing not to drink alcohol. I know you aren't currently pregnant or planning to become pregnant, but you are in the primary childbearing years right now. If you change your mind about pregnancy or discover in the future that you are pregnant, or you do begin to drink, please keep in mind that research has shown a link between drinking during pregnancy and the baby having an FASD. A child with an FASD can have physical and behavior problems, as well as cognitive problems (or, problems with the brain). These effects are caused by the alcohol, and they don't go away, although they can be treated. There is no known safe amount of alcohol to consume during pregnancy, and any type of alcohol can cause FASD.

Can I give you a brochure [or Web address, such as **www.fasdcenter.samhsa.gov**] *to take with you? This will explain more about FASD and how to have a healthy baby. Even if you aren't planning to become pregnant, you could share it with a friend or family member who is."*

*****

If asked: Why is there no known safe amount of alcohol that a woman can have during pregnancy?

Answer: The amount of alcohol required to damage an unborn baby differs based on the individual. Things like how much alcohol a woman drinks, how often she drinks during pregnancy, and which trimesters she drinks in all play a part. It also depends on genetics, whether the woman smokes or uses other drugs, her general health and nutrition, her age, and her levels of stress or trauma. That's why the Surgeon General recommends that pregnant women not drink any alcohol at all.

If asked: What kinds of alcohol should I avoid?

Answer: All alcohol can harm a baby while you're pregnant, not just beer, wine, and hard liquor. Wine coolers and 'alco-pops' also count. Anything with alcohol. Even some over-the-counter medications have a lot of alcohol in them; if you're pregnant or thinking of becoming pregnant, you should be careful about those, too.

If asked: Where can I find more information about FASD?

Answer: In addition to the SAMHSA FASD Center for Excellence (**www.fasdcenter.samhsa.gov**), the CDC (**http://www.cdc.gov/ncbddd/fasd/index.html**) provides extensive information about FASD.

Whether asked for more information or not, the universal AEP prevention message should be accompanied by appropriate awareness materials, either in print or via a Web address. The SAMHSA FASD Center for Excellence provides a series of consumer fact sheets called *What You Need to Know* that provides helpful information about how to have a healthy baby. Appendix C, *Public and Professional Resources* on FASD, has links to additional information resources.

At the same time, counselors should keep in mind with universal AEP prevention that, in some situations, women may deny using alcohol, but a combination of signs and symptoms suggest otherwise. In such cases, it may be prudent to re-screen frequently (Taylor, Bailey, Peters, & Stein, 2009).

Selective Prevention

The following section discusses two brief interventions for AEP prevention that are appropriate with women of childbearing age who report alcohol use but have only one of the two indicators for an indicated intervention; they are either pregnant but do not screen positive for at-risk alcohol use, or they screen positive for at-risk alcohol use but are not pregnant. These are organized in terms of the time required to perform the intervention effectively. As with universal prevention, each of these approaches should be accompanied by appropriate FASD information material, such as the *What You Need to Know* fact sheets, either in hard copy or through a Web link.

FLO (Feedback, Listen, Options)

1.	Provide **F**eedback about screening results. If possible, confirm the results with additional screening and provide information about recommended drinking limits. (For women who are—or are planning to become—pregnant, the ideal goal is abstinence.)
2.	Ask clients for their views about their own drinking and **L**isten carefully to encourage their thinking and decision-making process.
3.	Provide medical advice, and negotiate a decision about **O**ptions clients can pursue, including establishing a goal and developing an action plan.

Source: Higgins-Biddle, J., Hungerford, D., & Cates-Wessel, K. (2009). *Screening and brief interventions (SBI) for unhealthy alcohol use: A step-by-step implementation guide for trauma centers.* Atlanta: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. [Parenthetical in #1 added.]

The first selective intervention, called 'FLO' for short, is a simple, three-step approach (see box below). An example of using the FLO approach with a client is illustrated in Vignette #1 in Part 1, Chapter 3 of this TIP.

The second selective intervention, FRAMES, is a more established and slightly more detailed method for motivating a client toward change, and has demonstrated positive results in brief intervention situations (Miller & Sanchez, 1994; Miller & Rollnick, 2002). See the box on the following page.

Each of these brief interventions discusses 'action plans' or strategies for changing alcohol-related behaviors. For counselors who are not already well-versed in substance use-related change strategies, NIAAA has provided a brief guide to simple change strategies in the publication *Helping Patients Who Drink Too Much* (2007). Basic strategies to discuss with the client can include:

- What specific steps the client will take (e.g., not go to a bar after work, measure all drinks at home, alternate alcoholic and non-alcoholic beverages);
- How drinking will be tracked (diary, kitchen calendar);
- How the patient will manage high-risk situations; and

FRAMES

F	**Feedback** Compare the patient's level of drinking with drinking patterns that are not risky. She may not be aware that what she considers normal is actually risky (*or that **any** consumption during pregnancy creates risk*).
R	**Responsibility** Stress that it is her responsibility to make a change.
A	**Advice** Give direct advice (not insistence) to change her drinking behavior.
M	**Menu** Identify risky drinking situations and offer options for coping.
E	**Empathy** Use a style of interaction that is understanding, non-judgmental, and involved.
S	**Self-efficacy** Elicit and reinforce self-motivating statements such as, "I am confident that I can stop drinking." Encourage the patient to develop strategies, implement them, and commit to change.

Source: Miller, W. R., & Rollnick, S. (2002). *Motivational interviewing: Preparing people for change.* (2nd ed.) New York, NY: Guildford Press. [Italics in "Feedback" added.]

- Who might be willing to help the client avoid alcohol use, such as a significant other or a non-drinking friend.

Indicated Prevention: Alcohol Screening and Brief Intervention (SBI)

Alcohol Screening and Brief Intervention (SBI) is a workbook-based brief intervention that is appropriate with women of childbearing age who screen positive for at-risk alcohol use and are pregnant. SBI generally takes 10 to 15 minutes to complete, and has been shown to positively impact abstinence rates and key subsequent health factors in the newborn, including higher birth weight/length and lower mortality (O'Connor & Whaley, 2007).

The WIC Project Care: Health and Behavior Workbook was originally developed for Women, Infants and Children (WIC) programs, which provide support to current and expecting mothers, but the workbook can be used across settings. It is crafted in very simple language and uses traditional brief intervention techniques, including education and feedback, cognitive–behavioral procedures, goal-setting, and contracting. The care provider should go through the workbook *with* the client. As with both universal and selective prevention, the SBI approach should be accompanied by appropriate FASD print materials or a relevant and reliable Web link for further information.

The workbook can be downloaded for free in multiple languages from the WIC Web site: **http://www.phfewic.org/Projects/Care.aspx**

Providing Intervention/Treatment: Additional Factors to Consider

The following are factors to keep in mind when delivering a brief intervention for AEP prevention, as well as when delivering full substance abuse treatment (for agencies that are able to offer such care).

- Selective and indicated prevention services should be delivered by someone with motivational interviewing (MI) skills if at all possible. While a detailed discussion of MI techniques is outside the scope of this TIP, SAMHSA provides a Web site (**http://www.motivationalinterview.org/**) that contains extensive materials and training resources for providers looking to develop their MI skills. See also TIP 35, *Enhancing Motivation for Change in Substance Abuse Treatment* (SAMHSA, 1999).
- Consider the woman's age and circumstances, and how these impact intervention/treatment. For example, life factors and obstacles to abstinence (family responsibilities, work, other children, etc.) will probably be very different for a teen vs. an older woman.
- Consider cultural context, as well; the cultural factors that impact treatment may be very different for an African-American, Hispanic/Latina, Asian-American, or Native-American woman (or a woman of any other minority) than for a Caucasian woman.
- Be willing to make modifications (e.g., frequency, duration) to maximize opportunities for prevention and recovery.
- Include and engage families in treatment, including significant others, grandparents, guardians, and custodians.
- Include relapse prevention.
- Include family support skills.
- Consider additional counseling factors:
  - Parenting skills (that work for both the parent and the child)
  - Trauma and abuse
  - Co-occurring mental health issues
- Using a calendar with a client who is already pregnant may help her differentiate when she found out she was pregnant from when she actually became pregnant. She may have consumed alcohol for some time before knowing of the pregnancy, and showing that the drinking occurred even before she knew she was pregnant can help her feel less pressured and alleviate feelings of guilt. Clients may feel guilty and not tell the whole truth (or even withhold the truth). This means that getting an accurate picture of alcohol use may require multiple screenings. It is critical to build trust over several sessions. [Vignette #4 in Part 1, Chapter 3 demonstrates the use of a calendar with a client.]
- Watch for clients who 'shut down' on the topic of alcohol, and be understanding if the client experiences a sense of panic

Ensuring Effective Contraception

A woman who drinks alcohol at risky levels may not always follow prescribed procedures for effective contraception (Astley et al., 2000b). Review contraception use with her to ensure that she has full contraceptive coverage every time she has sexual intercourse. This might include providing secondary, back-up, or emergency contraception methods. For example, along with oral contraceptives, advise her to use condoms, which have the added benefit of reducing sexually transmitted diseases.

Source: *Division of Women's Health Issues. (2006). Drinking and reproductive health: A Fetal Alcohol Spectrum Disorders prevention tool kit. Washington, DC: American College of Obstetricians and Gynecologists.*

about what she may have unintentionally done to her baby.

- If the client is not pregnant but is drinking, and is not resistant to talking about contraception, qualified professionals can consider adding a discussion of effective contraception (see box, "Ensuring Effective Contraception") to discussions about drinking reduction.

Approaches to Resistance

With any approach to AEP prevention, counselors should keep in mind that, while a female client may feel safe enough to share about her alcohol use, she may not be ready to take the next step of comprehensive assessment and treatment (Astley et al., 2000b). A woman may present as resistant, reluctant, resigned, or rationalizing. The publication *Substance Abuse During Pregnancy: Guidelines for Screening* (Taylor et al., 2009) provides guidance on meeting these various forms of resistance. In addition, see the box below.

Procedures for Referral

If you believe, based on screening and interaction during intervention, that your client requires assistance that is best delivered in another care setting (or treatment in another setting becomes necessary due to factors such as criminal justice or social service involvement), you should discuss the benefits of treatment with the client and offer to provide her with a referral to a local substance abuse treatment center or other appropriate provider. A general list of treatment facilities can be searched through The SAMHSA Treatment Locator (**http://findtreatment.samhsa.gov**). Additional referral possibilities include the following:

- County substance abuse services;

Resistant, Reluctant, Resigned, or Rationalizing

• Resistant: "Don't tell me what to do."
Provider Response: Work with the resistance. Avoid confrontation and try to solicit the woman's view of her situation. Ask her what concerns her about her use and ask permission to share what you know, and then ask her opinion of the information. Accept that the process of change is a gradual one and it may require several conversations before she feels safe about discussing her real fears. This often leads to a reduced level of resistance and allows for a more open dialogue. Try to accept her autonomy but make it clear that you would like to help her quit or reduce her use if she is willing.
• Reluctant: "I don't want to change; there are reasons."
Provider Response: Empathize with the real or possible results of changing (for example, her partner may leave). It is possible to give strong medical advice to change and still be empathetic to possible negative outcomes to changing. Guide her problem-solving.
• Resigned: "I can't change; I've tried."
Provider Response: Instill hope, explore barriers to change.
• Rationalizing: "I don't use that much."
Provider Response: Decrease discussion. Listen, rather than responding to the rationalization. Respond to her by empathizing and reframing her comments to address the conflict between wanting a healthy baby and not knowing whether "using" is really causing harm.

Sources: Taylor, P., Bailey, D., Peters, R., & Stein, B. (2009). *Substance abuse during pregnancy: Guidelines for screening.* Olympia, WA: Washington State Department of Health.
DiClemente, C. C. (1991). Motivational interviewing and stages of change. In W. R. Miller & S. Rollnick (Eds.), *Motivational Interviewing: Preparing People to Change Addictive Behaviors* (pp. 191- 206). New York: Guilford.

Targeted Referral Options

Non-Pregnant Women: Project CHOICES

Project CHOICES is an evidence-based intervention (Project CHOICES Intervention Research Group, 2003; Floyd et al., 2007) that targets women at risk of having an AEP *before* they become pregnant. The goal is to reduce drinking and/or prevent pregnancy through contraception.

The target population for Project CHOICES is women ages 18 to 44 who are sexually active and drinking alcohol at risk levels. The model uses a four-session intervention approach based in MI methods, and discussions in each session are tailored to the client's self-rated readiness to change and interest in discussing alcohol use or contraception.

Project CHOICES programs exist in multiple settings, including residential and outpatient substance abuse treatment, community mental health treatment, jails, and community-based teen programs for girls. Eligibility criteria include 1) self-report of being sexually active, 2) being non-pregnant (but able to conceive), 3) high-risk drinking (8 or more drinks per week or 4 or more drinks in one occasion) in the past 30 days, 4) ineffective use of or no contraception, and 5) not currently trying to become pregnant or planning to try in the next 6 months.

Intervention Components:

- Four MI-based counseling sessions, including personalized feedback of risk, motivation to change one or both risk behaviors, decreasing temptation to engage in risk behaviors and increasing confidence to avoid them, goal-setting, and change planning; and
- One contraceptive counseling visit.

The CDC provides additional information about Project CHOICES at **http://www.cdc.gov/ncbddd/fasd/research-preventing.html**.

Pregnant Women: Parent-Child Assistance Program (PCAP)

The Parent-Child Assistance Program (PCAP) is a scientifically validated (Grant et al., 2005) paraprofessional case management model that provides support and linkages to needed services to women for 3 years following enrollment. The goal is to reduce future AEP by increasing abstinence from alcohol and drug use and/or improving regular use of reliable contraception among enrollees.

The target population for PCAP is pregnant or post-partum women (up to 6 months) who have had an AEP and will self-report drug and/or alcohol use during the target pregnancy. The model is based in Relational Theory, the Stages of Change, and harm reduction.

PCAP programs exist in a variety of settings, including substance abuse treatment and family support centers. Eligibility criteria include self-report of heavy alcohol or illicit drug use during pregnancy and ineffective or non-engagement with community social services.

Intervention Components:

- Paraprofessional home visitation;
- Goal-setting;
- Case management targeting alcohol use and contraception use; and
- Linkages to community services and programs.

Case management is provided at least twice monthly for up to 3 years following initial entry into the program.

To learn more about PCAP, including contact information, background materials, an implementation guide, and relevant forms and materials, visit **http://depts.washington.edu/pcapuw/**.

- 12-Step programs;
- Hospital treatment programs;
- Mental health programs; and
- Special pregnancy-related programs, which can be identified through your state health department by calling 800-311-BABY (2229), or 800-504-7081 for Spanish.

Programs throughout the United States have worked and are working directly with the SAMHSA FASD Center for Excellence to implement SBI (summarized above), Project CHOICES, or the Parent-Child Assistance Program (PCAP) (both summarized in the box "Targeted Referral Options," previous page). A program near you can be considered a source for possible referral or for guidance on locating a similar program. Please contact the FASD Center for Excellence for current program contact information (**www.fasdcenter.samhsa.gov**). Your local FASD State Coordinator may also be able to provide guidance on appropriate referrals. The National Association of FASD State Coordinators can be con¬tacted via the SAMHSA FASD Center for Excellence Web site: **http://fasdcenter.samhsa.gov/statesystemsofcare/nafsc.aspx**.

The feasibility of fully implementing SBI, Project CHOICES, or PCAP in your agency will depend on your staff skill set, your collaborative network, your funding, and a variety of other factors that are examined in greater detail in the Administrative section (Part 2) of this TIP.

Providing a Referral: Additional Factors to Consider

- Discuss possible strategies for the client to stop consuming alcohol; for example, individual counseling, 12-Step programs, and other treatment programs. Studies have shown that people given choices are more successful in treatment (Taylor et al., 2009).
- Use an advocate or special outreach services, if available, such as PCAP or Maternity Support Services (Taylor et al., 2009). Refer to Appendix C, *Public and Professional Resources on FASD*, for additional sources of information on community supports.
- Obtain information about costs, which health plans cover alcohol services (e.g., Medicaid, Medicare, state assistance, and public programs), who to contact to refer a patient, the phone numbers, and the necessary procedures for enrollment. This will allow you to tailor the referral to the client's needs and health insurance coverage (Higgins-Biddle, Hungerford, & Cates-Wessel, 2009).
- Identify the types of services available in your area (e.g., cognitive–behavioral, 12-Step, Motivational Enhancement Therapy) and the types of modalities (e.g., in-patient, outpatient), and prepare short descriptions of the available options so patients can understand the differences among alternative approaches (Higgins-Biddle et al., 2009).
- If possible, help the client make an appointment while she is in your office. If the woman is unwilling to make that commitment, ask if she would like some information to take with her if she should change her mind. Schedule the next visit, continue to maintain interest in her progress, and support her efforts to change. Monitor and follow up on any

Helping Your Clients Receive Culturally Competent Services

This TIP, like all others in the TIP series, recognizes the importance of delivering culturally competent care. Cultural competency, as defined by HHS, is…

"A set of values, behaviors, attitudes, and practices within a system, organization, program, or among individuals that enables people to work effectively across cultures. It refers to the ability to honor and respect the beliefs, language, interpersonal styles, and behaviors of individuals and families receiving services, as well as staff who are providing such services. Cultural competence is a dynamic, ongoing, developmental process that requires a long-term commitment and is achieved over time" (U.S. Department of Health and Human Services, 2003, p. 12).

This section discusses national information resources that are available on the topic of cultural competence or for providing care to specific cultural groups (listed alphabetically). However, the absence of a specific cultural group from this section is not meant to suggest that cultural competency is not an issue for that population. Individuals from all cultural backgrounds deserve respect and attention in a treatment environment, and the significance of culture needs to be recognized in relation to many different areas of a person's life; race, ethnicity, gender, sexual orientation, age, socioeconomic status, language, etc.

Chapter 3 of this TP, *Clinical Vignettes*, contains additional information on the essential elements of culturally competent counseling.

Hispanic/Latin Populations

If your agency is not fully capable in serving Hispanic/Latin clients or a Hispanic/Latin client requests culturally specific services, the National Council of La Raza provides a search tool (**http://www.nclr.org/index.php/nclr_affiliates/affiliate_network/**) that can direct clients to over 300 community-based organizations that provide a variety of health and general services for Hispanic/Latin populations.

In addition, SAMHSA's National Hispanic & Latino Addiction Technology Transfer Center (ATTC) offers a variety of products and resources focused on the health needs of Hispanics and Latinos. Visit their Web site at **http://www.attcnetwork.org/regcenters/index_nfa_hispaniclatino.asp**.

Native Populations

If your agency is not fully capable in serving native clients or a native client requests culturally specific services, the Indian Health Service (IHS) provides an interactive search map (**http://www.ihs.gov/findhealthcare/**) that can be used to find an IHS, Tribal, or Urban Indian Health Program (UIHP) facility. This search engine scans a variety of settings, including hospitals, behavioral health settings, village clinics, and school health facilities.

If you are unable to locate services through the map, the Health Resources and Services Administration (HRSA) provides the HRSA Health Center locator (**http://findahealthcenter.hrsa.gov/Search_HCC.aspx**) to determine if there are other culturally specific services available in your area.

Cultural Competency Training/Learning

The SAMHSA FASD Center for Excellence can provide training or technical assistance (TA) on cultural competency topics, or can put your agency in touch with a nearby specialist. Training and TA request forms can be accessed online (**http://www.fasdcenter.samhsa.gov**). Chapter 3 of this part of the TIP, Clinical Vignettes, also contains a checklist of core competencies for the culturally sensitive counselor.

In addition, the HRSA's Culture, Language and Health Literacy page (**http://www.hrsa.gov/culturalcompetence/index.html**) provides links to a range of resources on cultural competence when serving clients of differing cultures, genders, and sexual identities.

co-existing psychiatric conditions (Taylor et al., 2009).

- Maintain communication with the substance abuse treatment or other provider to monitor progress (Taylor et al., 2009).
- If immediate substance abuse treatment or other support is not available, the counselor or designated staff might meet with the woman weekly or bi-weekly to express concern and to acknowledge the seriousness of the situation (Taylor et al., 2009).

Working with Women Who May Have an FASD

When working with women of childbearing age, counselors may encounter clients who exhibit symptoms or characteristics suggesting that they themselves have an FASD. Research has identified intergenerational FASD as a pattern (Kvigne et al., 2003; May et al., 2005). Verifying the presence of an FASD is a process of observation, interviewing, and additional screening that takes time. The guidelines provided in the next chapter, *Addressing FASD in Treatment*, can prove helpful for counselors who want to pursue verification of a possible FASD in the client, and/or wish to modify their approach to delivering prevention or treatment/referral accordingly.

For more information on AEP prevention...

Vignettes 1–4 in Part 1, Chapter 3 illustrate scenarios where a counselor practices AEP prevention approaches. In addition, Part 3, the online literature review, also contains further discussion of screening and prevention interventions.

2 Addressing FASD in Treatment

IN THIS CHAPTER

Introduction

Value of Addressing FASD

Although the evidence base for effective substance abuse/mental health interventions with individuals who have or may have an FASD is limited (Premji, Benzies, Serrett, & Hayden, 2006; Paley & O'Connor, 2009), research has demonstrated that this population can and does succeed in treatment when approaches are properly modified, and that these modifications can lead to improved caregiving attitudes and reduced stress on family/caregivers as well as providers (Bertrand, 2009).

For the counselor, building competence with FASD has the obvious value of enhancing professional skills, as the counselor can provide FASD-informed care. For the client, addressing FASD has the potential to enhance the treatment experience for both the individual with an FASD and those around him or her, increase retention, lead to improved outcomes, reduce the probability of relapse (thus helping to break the cycle of repeated treatment, incarceration, displacement), and increase engagement rates in aftercare services. Access to FASD-informed interventions and accommodations, like those discussed in this chapter, has the potential to create protective factors for the client that can reduce secondary disabilities (Streissguth et al., 2004) and has been shown to lead to better outcomes (Bertrand, 2009).

For the client, addressing FASD provides an additional route to possible treatment success. Individuals with an FASD are a largely hidden population, yet these individuals frequently need services for substance abuse, and, especially, mental health (Streissguth et al., 1996). For every client that did not return for appointments, seemed noncompliant or resistant with no clear explanation of why, or just didn't seem to 'get it,' a knowledge of FASD could be an extra clue that helps solve that puzzle and enable success for both the client and the program.

Be Willing…

To effectively serve individuals who have or may have an FASD, what is needed most is a counselor who is willing. For many individuals with an FASD, it is not that they *can't* do the things necessary to succeed in treatment. Rather, it's that no one is willing to develop the understanding needed to help them succeed. While individuals with an FASD do present unique challenges, a willing counselor can make the difference between treatment success and treatment 'failure.'

- ***Be willing*** to understand the brain-based disabilities that are characteristic of these disorders: With any diffuse brain damage, including the damage that can result from prenatal alcohol exposure, some of the effects are permanent, and one cannot assume or teach the usual decision-making and self-care capabilities.
- ***Be willing*** to observe physical and behavioral factors and consider possibilities beyond defiance, noncompliance, or other more commonly diagnosed symptoms.
- ***Be willing*** to meet the client where they are and enable their growth.
- ***Be willing*** to set aside the false view that, because an FASD is permanent, "nothing can be done." Individuals with an FASD can and do respond positively to treatment that is modified to meet their unique needs.
- ***Be willing*** to develop treatment plans for this population with the identification and addressing of secondary disabilities as a built-in expectation, as research has shown that individuals with an FASD exhibit a unique prevalence of co-occurring disorders (O'Connor et al., 2002; Astley, 2010; Pei, Denys, Hughes, & Rasmussen, 2011; Kodituwakku & Kodituwakku, 2011).
- ***Be willing*** to redefine success and consider multiple treatment options and make modifications (frequency, duration, cultural issues, client strengths, etc.) to maximize the client's opportunities for recovery.
- ***Be willing*** to stretch the schedule. Success with a client who has an FASD can take longer, but it is achievable. Interventions should aim to "…support the life path of an individual with disabilities in a positive direction over time" (Olson, Oti, Gelo, & Beck, 2009).

It is important to note that this TIP is not encouraging counselors to forego the primary treatment issue that brought the client to their setting in the first place, in favor of treating FASD. This chapter is only providing a process for identifying FASD as a possible barrier to successfully addressing the primary treatment issue, and making appropriate modifications to your treatment approach to maximize the potential for positive outcomes. Even if the cognitive or behavioral barriers that you identify through this process do not ultimately result in a diagnosis or positive assessment for an FASD, these are still functional impairments presenting barriers to treatment, and thus the process remains valuable.

Identifying the Need for FASD Assessment, Diagnosis, and Services: Suggested Steps

The step chart on the next page illustrates a six-stage process that counselors can implement with clients for whom there are indications of an FASD. These steps will form the outline for the remainder of this chapter.

1. The Starting Point: Observing Indicators

Identifying Barriers and Causes

If there are indications of an FASD in the form of maladaptive behaviors, Step 1 represents a critical intermediate process: Be willing to consider the *root cause* of the behavior rather than just responding to the behavior. The

easiest way to think of Steps 1 and 2 is that Step 1 is the observation of a treatment barrier or group of barriers, Step 2 is the examination of a possible root cause (or causes).

So, in Step 1, you have a client who is not doing well in treatment, and you have exhausted your normal protocol of approaches for improving the efficacy of the treatment relationship. Since individuals with an FASD are at an increased risk of having substance use or mental health issues in the first place (Streissguth et al., 1996; Astley, 2010), what this step asks you to do is take a step back and consider whether the maladaptive behaviors that you are observing (e.g., frequently missed appointments) match the profile of an individual who may have an FASD (i.e., poor time management skills, memory problems).

When working with an individual who has an FASD, a counselor would be likely to observe problem indicators in the following functional domains:

- Planning/Temporal Skills
- Behavioral Regulation/Sensory Motor Integration
- Abstract Thinking/Judgment
- Memory/Learning/Information Processing
- Spatial Skills and Spatial Memory
- Social Skills and Adaptive Behavior
- Motor/Oral Motor Control

Problems in these domains will likely show up as deficits that interfere with treatment success, including:

- Inability to remember program rules or follow multiple instructions.
- Inability to remember and keep appointments, or to get lost on the way there.
- Inability to make appropriate decisions by themselves about treatment needs and goals.
- Inability to appropriately interpret social cues from treatment professionals or other clients.
- Inability to observe appropriate boundaries, either with staff or other clients.
- Inability to attend to (and not disrupt) group activities.

- Inability to process information readily or accurately.
- Inability to 'act one's age.'

When indicators occur in any these domains (and particularly when they occur across multiple domains), it is worthwhile to apply the FASD 4-Digit Code Caregiver Interview Checklist (Astley, 2004b) in Step 2 to determine if there is sufficient cause to 1) pursue evaluation for an FASD with this client, and 2) modify treatment to account for the client's functioning in these areas.

2. Functional Observation and History/Interviewing

An Appropriate Approach to Observation and Interviewing

If you have decided to move on to a fuller examination of the possible presence of an FASD based on indicators observed in Step 1, it is important to approach the topic with care and sensitivity. For the client, discussion of a possible FASD can cause feelings of shame, or possibly even anger or disbelief, about being identified with a "brain disorder." For the family of the individual, particularly for a birth mother, suggesting the possible presence of an FASD can lead to feelings of guilt or a feeling of being 'blamed,' and a perception that service systems are unhelpful or even a negative experience. It is critical for a counselor to take a no-fault, no-shame approach to the topic of FASD, continually reassuring the individual and the family that you are examining the possibility of an FASD only as a way to achieve the best possible treatment outcome.

The FASD 4-Digit Code Caregiver Interview Checklist

The FASD 4-Digit Code Caregiver Interview Checklist provided below is from the FASD 4-Digit Diagnostic Code (Astley, 2004b). The checklist is also reproduced in Appendix D, and can be considered for reproduction and inclusion in your treatment file for clients where you believe a form of FASD may be present.

However, please note: **This checklist is not presented as a validated FASD screening instrument**. It is simply provided as a tool that can be used over time to note typical problem areas for someone who might have an FASD (i.e., building a profile of FASD), and provides information that you can combine with your clinical judgment to make a better-informed decision about whether to direct a client toward a more extensive FASD assessment or diagnosis.

It should also be noted that the behaviors identified on this checklist can indicate other disorders, as well. Individuals with an FASD are frequently misdiagnosed (Greenbaum et al., 2009). Given their symptoms, they may be described as meeting criteria for Attention Deficit/Hyperactivity Disorder (ADHD), Attention Deficit Disorder (ADD), Oppositional Defiant Disorder (ODD), adolescent depression, or bipolar disorder. It is possible for FASD to co-occur with any of these diagnoses, but it is also possible that a condition on the fetal alcohol spectrum may better describe the pattern of target symptoms than these other diagnostic terms. A differential and comprehensive diagnosis is essential, whether in-house or through referral, and the information gathered through this checklist can help to inform a diagnostic process.

In a profile of the first 1,400 patients to receive diagnostic evaluations for an FASD at the Washington State FAS Diagnostic & Prevention Network (FAS DPN), caregivers completing an interview with a professional based in part on this checklist demonstrated an impressive ability to differentiate the behavior profiles of children with FAS/pFAS, children with severe ARND (SE/AE), and

The FASD 4-Digit Code Caregiver Interview Checklist

Severity Score: Severity of Delay/Impairment (Displayed along left margin)

Circle: **0** = Unknown, Not Assessed, Too Young **1** = Within Normal Limits **2** = Mild to Moderate **3** = Significant

Severity	Caregiver Observations
	Planning/Temporal Skills
0 1 2 3	Needs considerable help organizing daily tasks _____
0 1 2 3	Cannot organize time _____
0 1 2 3	Does not understand concept of time _____
0 1 2 3	Difficulty in carrying out multi-step tasks _____
0 1 2 3	Other _____
	Behavioral Regulation/Sensory Motor Integration
0 1 2 3	Poor management of anger/tantrums _____
0 1 2 3	Mood swings _____
0 1 2 3	Impulsive _____
0 1 2 3	Compulsive _____
0 1 2 3	Perseverative _____
0 1 2 3	Inattentive _____
0 1 2 3	Inappropriately [high or low] activity level _____
0 1 2 3	Lying/stealing _____
0 1 2 3	Unusual [high or low] reactivity to [sound touch light] _____
0 1 2 3	Other _____
	Abstract Thinking/Judgment
0 1 2 3	Poor judgment _____
0 1 2 3	Cannot be left alone _____
0 1 2 3	Concrete, unable to think abstractly _____
0 1 2 3	Other _____
	Memory/Learning/Information Processing
0 1 2 3	Poor memory, inconsistent retrieval of learned information _____
0 1 2 3	Slow to learn new skills _____
0 1 2 3	Does not seem to learn from past experiences _____
0 1 2 3	Problems recognizing consequences of actions _____
0 1 2 3	Problems with information processing speed and accuracy _____
0 1 2 3	Other _____
	Spatial Skills and Spatial Memory
0 1 2 3	Gets lost easily, has difficulty navigating from point A to point B _____
0 1 2 3	Other _____

Severity	Caregiver Observations
	Social Skills and Adaptive Behavior
0 1 2 3	Behaves at a level notably younger than chronological age _____
0 1 2 3	Poor social/adaptive skills _____
0 1 2 3	Other _____
	Motor/Oral Motor Control
0 1 2 3	Poor/delayed motor skills _____
0 1 2 3	Poor balance _____
0 1 2 3	Other _____

Source: Astley, S. J. (2004). *Diagnostic guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code*, Third Edition. Seattle, WA: University of Washington. Accessed June 1, 2012 at **http://depts.washington.edu/fasdpn/pdfs/FASD-2004-Diag-Form-08-06-04.pdf**. Used with permission from the author.

children with moderate ARND (ND/AE) (Astley, 2010).

In addition, the box "Risk Assessment Questions" contains a group of questions developed at the FAS Community Resource Center in Tucson, Arizona. These questions can further assist providers seeking to determine whether an evaluation for an FASD is warranted.

3. Assessment (External or Through an In-House Assessment Team)

Assessment for the presence of an FASD is an interdisciplinary process best accomplished through a team approach. The sad reality is that the existing network of qualified assessment teams and facilities in the United States is insufficient to meet demand, and behavioral health experts have repeatedly observed the urgent need for an increase in FASD

Risk Assessment Questions

Yes/No	Additional Areas of Consideration
	Client History
Y N	Are there alcohol problems in family of origin?
Y N	Was the client raised by someone other than the birth mother?
Y N	Has the client ever been in special education classes?
Y N	Has the client had different home placements?
Y N	Has the client ever been suspended from school?
Y N	Has the client ever been diagnosed as ADHD?
	How many jobs has the client had in past 2 years? _____
Y N	Can the client manage money effectively?
	Are the client's friends older or younger (for an individual with an FASD, friends will tend to be younger due to lag between physical age and functional age)? _____

Adapted from: Kellerman, T. (2005). Recommended assessment tools for children and adults with confirmed or suspected FASD. Tucson, AZ: FAS Community Resource Center. Accessed June 5, 2012 at **http://come-over.to/FAS/AssessmentsFASD.htm**.

assessment, diagnosis, and treatment capacity (Institute of Health Economics, 2009; Interagency Coordinating Committee on FASD, 2011).

However, many substance abuse and mental health treatment settings may have an interdisciplinary staff team and/or sufficient referral relationships to attempt FASD assessment internally, creating an opportunity to help fill a gap in the behavioral health field. If this is the case with your agency, this section discusses some of the essential elements of FASD assessment, as well as available resources that can help your agency develop this staff capability. (The first interdisciplinary FASD diagnostic clinic [the Washington State FAS Diagnostic and Prevention Network (FAS DPN)] was established in Washington State in 1993 as part of a CDC-sponsored FASD prevention study [Clarren & Astley, 1997]. A comprehensive description of the interdisciplinary model used by the Washington State FAS DPN is presented by Clarren, Carmichael-Olson, Clarren, and Astley [2000]; see Appendix A: *Bibliography*). In addition, for sites that cannot provide FASD capacity internally, referral options do exist, and this section will provide information on accessing those resources.

In-House FASD Assessment: The Essential Elements

Effective in-house assessment for FASD is built on three core components: 1) building the right team, 2) accessing the right resources, and 3) gathering the right information.

Building the Right Team

FASD assessment, as will be explained below, involves gathering information and making evaluations in a variety of functional areas, and is an involved process that can overwhelm the client and his or her family. This necessitates a wide range of professional skill sets, not only to perform the various clinical and observational tasks, but also to help the client and family navigate the process smoothly. The box "In-House FASD Assessment: An Ideal Core Team" describes an ideal in-house FASD assessment team and its functions.

Part 2, Chapter 2 of this TIP outlines appropriate processes if these professionals need to be added and/or accessed through referral relationships.

Accessing the Right Resources

Appendix C, *Public and Professional Resources on FASD*, provides information and links for accessing FASD information and training from a variety of national and regional sources.

In-House FASD Assessment: An Ideal Core Team

Case Coordinator	• Reviews history and current stability • Assesses needs of individual and caregiver • Post-diagnosis, connects individual/family to positive supports • Is often a social worker, but in this case could be the role of the counselor
Psychologist[1] and Speech Language Pathologist	• Assess basic and higher levels of brain function
Physical Therapist, Occupational Therapist, or Vocational Rehabilitation Counselor	• Assesses motor and sensory issues (including sensory-motor integration, and balance and gait issues)

Physician	• Assesses dysmorphology, neurological findings, and basic health determinants • Also contributes to behavioral health profile
Family Navigator	• Helps the family through the process • Ideally is an actual caregiver of someone with an FASD • Ideally is available to help the family connect with parent support and other needed resources

Based on TIP consensus panel recommendations and *Canadian Guidelines for Diagnosis* (Chudley, Conry, Cook, Loock, Rosales, & LeBlanc, 2005).

[1] The psychologist should be trained to do neuropsychological testing.

Among these are two excellent resources for agencies seeking to develop FASD capabilities; the Washington State FAS DPN and the CDC's FASD Regional Training Centers (RTCs).

- One of the primary sites for FASD assessment and diagnosis in the United States is the Washington State FAS DPN, based at the University of Washington in Seattle. Established in 1993 through Washington State Senate Bill 5688 and support from the CDC, March of Dimes, Chavez Memorial Fund, and the Washington State Department of Social and Health Services, the Washington State FAS DPN provides FASD diagnostic services as well as training in FASD. Training resources include the FASD 4-Digit Diagnostic Code Online Course and a 2-day FASD Diagnostic Team training for interdisciplinary clinical teams (or individual clinical team members) seeking to establish FASD services in their community. Visit the FAS DPN's homepage (**http://depts.washington.edu/fasdpn/**) to find out more about their services.
- The CDC's RTCs develop, implement, and evaluate educational curricula regarding FASD prevention, identification, and care, and incorporate the curricula into training programs at each grantee's university or college, into other schools throughout their regions, and into the credentialing requirements of professional boards. Visit the CDC's RTC homepage (**http://www.cdc.gov/ncbddd/fasd/documents/flyerfasd_rtcs.pdf**) to find out about currently funded RTC sites and available services.

Gathering the Right Information

A useful tool that your team can use to gather and organize the necessary information to support a formal FASD diagnosis is the *New Patient Information Form*. This form was developed by the Washington State FAS DPN and is part of the *Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code* (Astley, 2004b, Third Edition, pp. 103-114). If your agency decides to refer a client for an FASD diagnosis, this information will provide a necessary foundation for the diagnostic process. The *New Patient Information Form* can be downloaded for free from (**http://depts.washington.edu/fasdpn/htmls/diagnostic-forms.htm**).

In addition to basic information about the client and your agency, the *New Patient Information Form* provides a template for gathering information in the critical areas of Growth; Physical Appearance and Health; Neurological Issues; Attention Deficit and

Hyperactivity; Mental Health Issues; School Issues; Alcohol Exposure; Information About the Patient's Biological Parents; Medical History of the Biological Family; Pregnancies of Birth Mother; Pregnancy, Labor, and Delivery of this Patient; List of Professionals Currently Involved in Patient's Care; Placements (foster, adoptive, etc.); and What to Bring to the [diagnostic] Clinic.

To further ensure collection of appropriate information and build staff knowledge and capabilities related to FASD, it will be valuable for your team to become familiar with the basic guidelines of the most widely used diagnostic approaches to the various disorders in the spectrum. A comprehensive comparison of the current FASD diagnostic systems is presented in a chapter entitled "Diagnosing FASD" (Astley, 2011), and is reprinted in Appendix E, *Comparison of Current FASD Diagnostic Systems* with the author's permission.

External: Assessment and Diagnosis

The reality for many programs will be that, for reasons of cost and/or lack of community resources, building an in-house FASD assessment team or diagnostic capability will be unrealistic. If this describes your agency, the FASD diagnosis and training sites discussed under *Accessing the Right Resources*, above, should be accessed so that you can refer your client to an appropriate provider. Agencies can also use the **Resource Directory** (**http://www.nofas.org/resource-directory/**) provided by the National Organization on FAS (NOFAS) to help locate FASD-related services.

At the same time, referral for assessment and diagnosis should be paired with treatment modifications and accommodations that are discussed in the next section. This can be done with or without a formal diagnosis of a form of FASD. If you and your clinical team have identified symptoms indicating an FASD through Steps 1 and 2 of this chapter, the methods discussed in the next section can still help the treatment process.

Many providers will not have an existing relationship with the FASD assessment or diagnosis provider to whom they refer a client. In such cases, it is vital to actively assist the client through the transition and provide regular follow-up to ensure client satisfaction and full and open communication between agencies and with the client. (Also the client's family, if they are involved in treatment.) The box "Overview of the Diagnostic Process (As Performed by the FAS DPN)" summarizes the phases of the diagnostic process as performed

Overview of the Diagnostic Process (As Performed by the FAS DPN)

A comprehensive description of the FAS DPN interdisciplinary FASD diagnostic process is presented by Clarren et al. (2000).

Phase	Description
Phase 1	• Clinical intake: Caregivers complete a comprehensive "New Patient Information Form" prior to the clinic visit to report current concerns and developmental, social and alcohol exposure history. Past medical, educational, psychological, social, and legal records are also obtained. • Record review: Psychologist reviews all available medical, developmental, clinical, educational, and other records, and presents a case summary to the FASD diagnostic team on the day of the diagnostic evaluation. Clients 18 and older are referred elsewhere for their neuropsychological evaluation.

Phase	Description
Phase 2	• Psychometric screening/evaluation: Diagnostic team members (occupational therapist, psychologist, speech–language pathologist) screen/assess the patient's current neurobehavioral performance (e.g., language and communication, executive function, cognition, sensory–motor skills). • Physical examination: Physician examines diagnostic parameters of growth and facial dysmorphology (and general health, sleep problems, medications used, etc.). • Caregiver(s) interview: Physician and psychologist conduct a caregiver interview (up to 2 hours) using the 4-Digit Code Caregiver Interview checklist.
Phase 3	• Diagnosis and intervention recommendations: Diagnostic team reviews and synthesizes data, derives the 4-Digit Code, and generates intervention recommendations. • Diagnostic summary: Diagnostic team shares the diagnosis and intervention recommendations with caregiver(s) in a brief case conference. Adolescent and adult clients are included in the case conference. • Diagnostic summary report: Diagnosis, assessment results, and intervention recommendations are integrated into a comprehensive 6- to-8-page diagnostic summary report (**http://depts.washington.edu/fasdpn/pdfs/4-digit-medsum-web-2006.pdf**) and submitted to the patient's medical record. • Follow-Up Debriefing: A private follow-up debriefing is conducted with the caregiver (and client, if old enough) to discuss the impact of the diagnosis and review specific recommendations.

Table originally appeared in Jirikowic, Gelo, & Astley (2010) with minor modifications.

by the Washington State FAS DPN. The phases of this process are likely to be similar in other interdisciplinary FASD diagnostic clinics.

When the Client Already Has a Diagnosis of an FASD

If a client has already been diagnosed with an FASD at the time of presentation to your setting, the guidelines in the next section should automatically be considered. In addition, as indicated in the table *Overview of the Diagnostic Process* in the previous section, the diagnosis report may also be a source of intervention and modification guidelines and should be thoroughly reviewed by the counselor with the client (and the family, if involved in the treatment process). A comprehensive summary of the types of intervention recommendations provided in relation to 120 youths following their FASD diagnostic evaluations at the Washington State FAS DPN is provided by Jirikowic et al. (2010).

At the same time, further assessment by medical, mental, and allied health professionals may still be needed to determine the client's current level of function in important areas, particularly if the diagnosis occurred years earlier. "Refreshing" the functional information will help the counselor tailor the treatment plan and counseling strategies to the client's strengths, needs, and preferences. Forms of re-testing and assessment can include the following:

- Being familiar with any medications the client is taking and observing any behaviors or physical symptoms that might indicate the need to reevaluate medication use or dosage;
- Hearing and speech tests to identify any progress in communication or barriers

that may affect the client's treatment and ongoing recovery;

- Occupational therapy and physical therapy evaluations to assess the client's daily living skills and motor function, vocational skills, and preferences and possibilities;
- Determining current achievement levels in reading, spelling, and math; and
- Use of an appropriate, standardized interview or questionnaire to determine how the client compares to peers in receptive, expressive, and written communication; personal, domestic, and community daily living skills; and interpersonal relationships, play and leisure time, and coping skills.

4. Tailoring Treatment for Individuals with an FASD

Introduction

This section will discuss appropriate approaches to modifying treatment and/or making necessary accommodations for clients who exhibit indicators suggesting an FASD, or who show cognitive and behavioral barriers to treatment success, as identified in Steps 1 and 2 of this chapter.

This discussion is divided into two sections; 1) general principles for working with individuals who have or may have an FASD (regardless of age), and 2) specific considerations for adolescents who have or may have an FASD. The chapter then moves on to Step 5, *Working With the Family*, and Step 6, *Transition and Connection to Community Supports*.

As noted above, if the individual already has a diagnosis of an FASD, the diagnostic report may also include recommendations for appropriate interventions and modifications to treatment. The counselor should review this report thoroughly, if it is available.

General Principles for Working with Individuals Who Have or May Have an FASD

Safety Considerations

Safety is a primary health issue for individuals of all ages with an FASD (Jirikowic et al., 2010). Starting a treatment process without first addressing safety issues is futile and potentially dangerous: The clinician must first evaluate physical safety for the adolescent or adult with an FASD. This includes issues of violence, harm to self (such as self-mutilation) or others, victimization, adequate housing, and food. In typical adolescents and adults, psychiatric severity can be significantly reduced when co-occurring issues are treated together and mental health and substance abuse treatment are provided as an integrated program (Hser, Grella, Evans, & Huang, 2006).

For older individuals who have or may have an FASD, there are special safety considerations. This population has a number of risk factors for accidents and injury; poor decision-making, impulsivity, impaired motor coordination, working memory, attention, emotional and sensory regulation, and susceptibility to peer pressure. Even seemingly routine tasks like crossing the street safely may be impossible for those who are more severely affected. Other examples of possible safety and health concerns in adolescents and adults with an FASD are remembering medication schedules, decisions about legal and illegal substances, driving, and risk-taking situations in which poor social problem-solving (McGee, Fryer, Bjorquist, Mattson, & Riley, 2008), impulsivity, and peer pressure combine to compromise safety.

Vignette #9 in Part 1, Chapter 3 of this TIP elaborates the process of working with a caregiver to develop a personalized Safety Plan on behalf of an individual with an FASD. In addition, Appendix F, *Sample Crisis/Safety Plan*, contains a sample plan that has been

adapted from the work of the *Families Moving Forward Program* (**http://depts.washington.edu/fmffasd/**), and can be printed and used with a client and/or their family member(s)/caregiver(s).

Risk for Abuse

Children with physical, psychological, and sensory disabilities—including FASD—are known to be more vulnerable to violence and maltreatment, or to be at a greater risk of these forms of abuse (Olivan, 2005). This vulnerability is brought about by a variety of factors, including dependence on others for intimate and routine personal care, increased exposure to a larger number of caregivers and settings, inappropriate social skills, poor judgment, inability to seek help or report abuse, and lack of strategies to defend themselves against abuse. Murphy and Elias (2006) report figures from the National Center on Child Abuse and Neglect indicating that children with disabilities are sexually abused at a rate 2.2 higher than that for children without disabilities. The United States Department of Justice reports that 68 to 83 percent of women with developmental disabilities will be sexually assaulted in their lifetimes, and less than half of them will seek assistance from legal or treatment services (Pease & Frantz, 1994). In a study of 336 males and females in treatment for alcohol abuse or dependence, more than 56 percent had also experienced childhood sexual or physical abuse (Zlotnick et al., 2006).

In one long-term study, 80 percent of young adults who had experienced abuse as a child met diagnostic criteria for at least one psychiatric disorder at age 21. These individuals exhibited many problems, including depression, anxiety, eating disorders, and suicide attempts (Silverman, Reinherz, & Giaconia, 1996). Other psychological and emotional conditions associated with abuse and neglect include panic disorder, dissociative disorders, attention-deficit/hyperactivity disorder, depression, anger, posttraumatic stress disorder, and reactive attachment disorder (Teicher, 2000; De Bellis & Thomas, 2003; Springer, Sheridan, Kuo, & Carnes, 2007).

Astley (2010) has documented a high prevalence of abuse, neglect, and multiple home placements among 1,400 patients identified with an FASD—70 percent were in foster/adoptive care and had experienced, on average, three home placements. In fact, in a separate study, Astley and colleagues (2002) identified a prevalence rate of FAS in foster care that was 10-times higher—1/100—than in the general population—1/1000. Children in foster care face a risk of maltreatment, which can affect their physical health and lead to attachment disorders, compromised brain functioning, inadequate social skills, and mental health difficulties (Harden, 2004). Another study among young women with FASD found that they had poor quality of life scores and high levels of mental disorders and behavioral problems relative to standardization samples and other at-risk populations (Grant et al., 2005).

Risk for Suicide

In addition, individuals with an FASD are at significant risk of suicide at all ages studied (Huggins et al., 2008). A person with an FASD may not appear to plan or execute a suicide attempt effectively; this is not indicative of the seriousness of the intent.

High Risk of Repeated Involvement with the Legal System

People with an FASD can have specific types of brain damage that may increase engagement in criminal activity (Kodituwakku et al., 1995; Page, 2001; Mattson, Schoenfeld, & Riley, 2001; Page, 2002; Moore & Green, 2004; Clark et al., 2004; Schonfeld, Mattson, & Riley, 2005; Schonfeld, Paley, Frankel, O'Connor, 2006; Brown, Gudjonsson, & Connor, 2011). These can include:

Suicide Intervention/Prevention for Individuals with an FASD

- Standard suicide assessment protocols need to be modified to accommodate neuropsychological deficits and communication impairments:
  - Instead of "How does the future look to you?" ask "What are you going to do tomorrow? Next week?" (Difficulties with abstract thought.)
  - The seriousness of the suicidal behavior does not necessarily equal the level of intent to die (lack of understanding of consequences).
- Obtain family/collateral input.
- Be careful about words used regarding other suicides or deaths.
- Intervene to reduce risk:
  - Address basic needs and increase stability.
  - Treat depression.
  - Teach distraction techniques.
  - Remove lethal means.
  - Increase social support.
- Do not use suicide contracts (impulsivity issues).
- Monitor risk closely.
- Reinforce and build reasons for living.
  - Be literal.
- Strengthen advocate-client relationship.

Source: Huggins, J. E., Grant, T., O'Malley, K., & Streissguth, A. (2008). Suicide attempts among adults with Fetal Alcohol Spectrum Disorders: Clinical considerations. *Mental Health Aspects of Developmental Disabilities, 11*(2), 33-42.

- Lack of impulse control and trouble understanding the future consequences of current behavior;
- Trouble understanding what constitutes criminal behavior (for example, a youth with an FASD may not see any problem with driving a car he knows was stolen if he wasn't the one who stole it);
- Difficulty planning, connecting cause and effect, empathizing (particularly if the experience is not explained in a very concrete way), taking responsibility, delaying gratification, and making good judgments;
- Tendency toward explosive episodes, often triggered by sensory overload, slower rates of processing the information around them, and/or feeling "stupid;"
- Vulnerability to peer pressure and influence (e.g., may commit a crime to please friends), and high levels of suggestibility; and
- Lower level of moral maturity (due in part to social information processing deficits).

The number of people in the criminal justice system with an FASD has not specifically been determined. Data are limited, and populations vary by state. In addition, few systems conduct any screening or can provide diagnosis. Streissguth and colleagues (2004) conducted an evaluation of 415 clinical patients with FASD at the University of Washington. Trouble with the law (including arrest, conviction, or otherwise) was reported in 14 percent of children and 60 percent of adolescents and adults with an FASD. In addition, Fast, Conry,

& Loock (1999) evaluated all youth referred to a forensic psychiatric assessment for FASD in Burnaby, British Columbia, Canada. Of 287 youths assessed, 67 (or 23 percent) were found to have an alcohol exposure-related diagnosis. Although this result should not be generalized to the entire prison population, it does reveal a possible disproportionate representation of individuals with an FASD in the juvenile justice system.

It is important for counseling professionals to consider a client's criminal history and any factors that place the client at risk for further criminal involvement. Because persons with an FASD have problems learning from experience, they may repeat crimes and cycle through the legal system multiple times.

Clinicians may encounter individuals with an FASD who are participating in court-ordered treatment. Such individuals need help navigating the legal system. The clinician can consult with the client's attorney and assist in educating him or her about FASD. In addition, the clinician can assist in finding resources to help the client understand any legal proceedings and requirements. The National Legal Aid & Defender Association (**http://www.nlada100years.org/**) or the American Bar Association (**www.americanbar.org**) may be able to identify resources at the local level.

Vulnerability of Individuals with an FASD
Individuals with an FASD are vulnerable not only to criminal activity but also to victimization (Freunscht & Feldman, 2011). Their poor judgment may lead them to associate with people who victimize them physically, emotionally, and financially. Their impulsivity may lead them into dangerous situations. Women with an FASD may get involved with negative associations for food, shelter, attention, or drugs (Page, 2003). In addition, their impaired sense of boundaries can lead to sexual victimization. Because of their unpredictable behavior, they may need 24-hour supervision (Streissguth, 1997).

Even with compensatory strategies, the person with an FASD may be less able to use judgment, consider consequences, or understand abstract situations (Kodituwakku, 2007; Astley, 2010; Freunscht & Feldman, 2011). Impulsivity is an ongoing issue. Social isolation and loneliness may drive the person to seek out any type of friendship and lead to victimization. A discussion or pursuit of safeguards for the person may be necessary:

- Recognize that victimization may occur, and keep vigilant for situations that may arise in the person's life.
- Role-play personal safety and specific scenarios that people face (e.g., who is a stranger vs. who is a friend) to allow the individual to practice taught skills and perhaps allow them to pursue safe activities (De Vos, 2003). Consider videotaping the client doing it right in the role-play, so he or she can watch it over and over, reinforcing the lesson. Watching the video also helps move the information from short-term memory to long-term memory. (In many cases, though certainly not all, long-term memory has been observed to function better than short-term memory for individuals with an FASD).
- Establish written routines and structured time charts, and have these where they are easily seen throughout the day.
- Provide a buddy system and supervision to help decrease opportunities for victimization.
- Consider a guardianship of funds to protect the individual. A trustee can ensure that the necessities of life are covered, including rent, food, clothing, and finding an advocate. The clinician may want to

include such provisions in the aftercare plan.
- Help the client find a healthy, structured environment in aftercare to help them avoid criminal activity.

Family Safety and Support

For all families caring for an individual with an FASD, or when parents themselves have an FASD, establishing family safety and support is vital. A crisis/safety plan should always be put in place (see Appendix F for an example *Crisis/Safety Plan* form). To stay safe and well-supported, it is important to help the client (and caregivers) identify available services, determine which ones are effective for them or their children, and understand how to work productively with service providers (Streissguth, 1997). (See Appendix G for a *Services and Supports Checklist* that can be reviewed with clients as a worksheet.)

For birth families in recovery, the counselor can help families cope with FASD during the recovery process. This is best done by building a protective environment for clients and their children. This may include helping them obtain safe, stable housing, assisting with daily living skills (such as bill paying and food shopping), and overseeing home situations. It is also important to establish a network of community service providers who will be available for aftercare to promote ongoing recovery and avoid relapse (Millon, Millon, & Davis, 1993).

For more information about this topic, see Step 6, *Transition and Connection to Community Supports*).

Modifying a Treatment Plan

Factors to Consider

When modifying a treatment plan for an individual who has or may have an FASD, the following should be considered:

- **Help the client adjust to a structured program or environment and develop trust in the staff**. Individuals with an FASD tend to be trusting (Freunscht & Feldman, 2011) and need a great deal of structure, but may have trouble adapting to changes in routine and to new people.
- **Share the rules early and often**. Put instructions in writing and remind the client often. Keep the rules simple and avoid punitive measures that most individuals with an FASD will not process. If a rule is broken, remind the client of the situation and help to strategize ways they can better follow the rule in the future.
- **Take a holistic approach**, focusing on all aspects of the client's life, not just the substance abuse or mental health issues. Include basic living and social skills, such as how to dress, groom, practice good hygiene, present a positive attitude, and practice good manners. Help the client develop appropriate goals within the context of his or her interests and abilities.
- **Provide opportunities to role-play or otherwise practice appropriate social behaviors**, such as helping others. Areas of focus may include impulse control skills, dealing with difficult situations such as being teased, and problem-solving.
- In an inpatient setting, **allow time** for the client to be stabilized and acquire the basic skills to cooperate with others before discussing his or her substance abuse or mental health issues. In an outpatient setting, it may help to develop a rapport with the client and establish trust and communication before addressing the primary treatment issue.
- **Assume the presence of co-occurring issues**. It is likely that a high percentage of people with an FASD have at least one co-occurring mental disorder (O'Connor

et al., 2002; Streissguth et al., 2004; Clark et al., 2004; Astley, 2010). In a study of 1,400 patients with FASD, Astley (2010) documented that 75 percent had one or more co-occurring disorders, with the most prevalent being ADHD (54 percent). In a study of 80 birth mothers of children with FAS, 96 percent had from one to nine mental disorders in addition to alcoholism (Astley et al., 2000b); the most common was phobia (76 percent). Forty-four percent of the women had mental disorders diagnosed by the age of 8 years.

- When possible, **include the family or caregivers in activities**, such as parent education about FASD and substance abuse and/or mental health, strategies for providing care for an individual with an FASD and a substance abuse or mental health problem (e.g., avoiding power struggles), and building the client's self-esteem. Help family and caregivers practice positive communication skills such as active listening, use of literal language, and avoiding "don't" (i.e., focusing on what *needs* to be done rather than what *should not* be done).
- **Include the client in treatment planning/modification**, and build family/caregiver meetings into the plan as well, with a clear purpose and agenda. Recognize that some family members may also have an FASD, and work with them accordingly.
- **Incorporate multiple approaches to learning**, such as auditory, visual, and tactile approaches. Avoid written exercises and instead focus on hands-on practice, role-playing, and using audio- or video-recording for playback/reinforcement of learning. Use multisensory strategies,

The Navigator

A person who has impaired vision is given a seeing eye dog. A person with impaired hearing is given an interpreter or a hearing aid. These external devices are necessary for the person with physical impairments to be able to function to maximum potential in life.

The person with an FASD has a physical impairment in the area of the brain, particularly the forebrain or frontal lobes, which regulate the executive functions. A navigator refers to the presence of another responsible person (parent, teacher, job coach, sibling) who can mentor, assist, guide, supervise, and/or support the affected person to maximize success (which may need to be redefined as the avoidance of addiction, arrest, unwanted pregnancy, homelessness, or accidental death).

Because some individuals with an FASD may appear to be bright and normal, the disability that is brain damage may only be apparent in test results, or in actions that place the person at serious risk. It is the risk of danger to the person and to others that makes a navigator such a useful and important concept. A navigator can seem like a form of enabling or an encouragement of co-dependency. More accurately, however, a navigator is an appropriate form of advocacy to ensure that the individual receives whatever assistive devices are needed for him or her to participate in life in as normal a capacity as reasonably possible.

For many individuals with an FASD, the navigator can be someone with whom they "check in" on a regular basis, or vice versa. For others, the navigator will play a more constant advocacy role, and may share the role with others. (See Vignette #9 for an example of a father playing the role of a navigator, and sharing the role with a coach and one of his son's relatives.)

Adapted from: Kellerman, T. (2003). External brain. Accessed June 5, 2012 at **http://come-over.to/FAS/externalbrain.htm**.

such as drawing, painting, or music, to assist the client in expressing feelings. These strategies take advantage of skills that many individuals with an FASD have. They can also help the client share difficult feelings that may be hard to talk about, such as fear and anger.

- **Consider sensory issues** around lighting, equipment sounds, and unfamiliar sensations and smells. Individuals with an FASD can be very sensitive to these environmental factors.
- **Arrange aftercare**, and encourage family/caregivers to participate in a support group to continue to learn parenting skills and to be encouraged in the recovery process (see Step 6, *Transition and Connection to Community Supports*).

Counseling Strategies

Due to the cognitive, social, and emotional deficits seen in FASD, counseling clients with these conditions requires adaptability and flexibility. Research data, clinical observation, and caregiver reports all suggest that it is crucial to tailor treatment approaches. Traditional approaches may not prove optimally effective, and more effort may be needed to convey basic concepts and promote a positive therapeutic relationship and environment. The following are recommendations designed to help providers:

- Set appropriate boundaries;
- Be aware of the client's strengths;
- Understand the impact of any abuse the client has experienced;
- Help the client cope with loss;
- Address any negative self-perception associated with an FASD;
- Focus on self-esteem and personal issues;
- Address resistance, denial, and acceptance;
- Weigh individual vs. group counseling;
- Consider a mentor approach; and
- Assess comprehension on an ongoing basis.

Boundaries

Establishing a trusting and honest relationship while maintaining boundaries is important with any client. Because persons with an FASD often lack social skills and have social communication problems (Kodituwakku, 2007; Greenbaum et al., 2009; Greenspan, 2009; Olson & Montague, 2011), they may breach boundaries by making inappropriate comments, asking inappropriate questions, or touching the counselor inappropriately. To set boundaries, it may help to have the client walk through the rules and expectations and demonstrate expected behavior. Frequent role-playing can help the client learn to apply concepts and figure out how to respond to various situations.

Persons with an FASD frequently experience difficulty with memory (Rasmussen, 2005; Riggins et al., 2012). Added to this, they may be able to repeat rules but not truly understand them or be able to operationalize them. Thus, it is important to review rules regularly. It is much more effective to limit the number of rules, review them repeatedly, and role-play different situations in which the person will need to recall the rules. Repetition is key.

Strengths

Many people focus on the deficits in persons with an FASD, but they also have many strengths. Some of these can be used in the treatment setting as part of counseling. Family may be a strength area: Parents report their children with FASD were engaged with their families and willing to receive—and even seek—help (Olson et al., 2009), as well as demonstrating a willingness to provide assistance with ordinary tasks (Jirikowic et al, 2008). Based on extensive clinical experience, Malbin (1993) identifies a number of other strength areas. For example, some people with

an FASD are quite creative. They can express themselves through art and music, which may prove more effective than traditional talk therapy. Other approaches may involve storytelling and writing. These techniques can also be used for practical matters, such as developing a poster with treatment goals. In addition, visual aids can assist by drawing on areas of relative strength, so drawn or pictured goals may aid recall better than a written or spoken list of instructions.

History of Abuse

Given the risk of abuse among persons with an FASD and among individuals with substance abuse and/or mental health issues, it is likely that a client with a combination of these will have some personal abuse history (Astley et al., 2000b). The counselor working with persons with an FASD needs to be sensitive to the possibility of childhood abuse and other forms of victimization, and their impact on the counselor–client relationship. A common theme that counselors need to be attentive to is *powerlessness*, a theme often reflected in the following types of client communications and behaviors:

- Clients undervaluing their own competencies.
- Clients viewing others' needs and goals as more important than their own.
- Clients' inability to obtain nurturance and support for themselves.
- Clients' feelings of depression, anger, and frustration about their lives.
- Clients' low expectations for their own success.

Loss and Grieving

All individuals with an FASD have experienced losses in their lives. The fact that they are not like their peers is a loss of the ability to be like everyone else. Some have lost the hopes and dreams of what they wanted to be. Others lose their family or a secure future. Some lose the opportunity for meaningful peer relationships and friendships. These losses can affect people in many ways and need to be addressed. The counselor can help to address these areas of loss through a number of strategies:

- Use active listening strategies, such as repeating what the person has said;
- Be honest;
- Raise awareness of experiences of separation and loss;
- Acknowledge and validate losses experienced;
- Acknowledge the client's feelings about loss;
- Avoid "good parent/bad parent" issues;
- Encourage communication; and
- Refer for further treatment (e.g., mental health) when necessary.

Self-Perception

Self-perception is a major issue with FASD. Despite the advent of the disease model, many people still view alcohol problems as a sign of moral weakness or a character flaw. This negative stereotype can be particularly severe in relation to pregnant women who drink, making the topic difficult to discuss (Salmon, 2008). Added to this, the negative judgment toward the mother may also be visited on the child. A counselor needs to be aware of this, and approach the issue carefully and sensitively if he or she suspects a client has an FASD.

Given their cognitive, social, and emotional deficits, persons with an FASD may think they are powerless to change. It is important to work through this issue with the client. They need to understand that they are not responsible for their disability and that they deserve respect. They also need to know that change is possible.

Self-Esteem and Personal Issues
The combination of abuse, loss, grief, and negative stereotypes can lead to self-esteem issues in any individual. Self-esteem is regularly an issue for individuals with an FASD (Olson, O'Connor, & Fitzgerald, 2001). Those who also have substance abuse or mental health problems face a double-edged sword: Their self-esteem can be damaged by their experience with an FASD and by their substance abuse or mental health issue. The clinician can use several strategies to help address self-esteem and personal issues:

- **Use person-first language**. An FASD may be part of who a person is, but it is not the person's entire identity. Someone can have an FASD, but nobody is an FASD.
- **Do not isolate the person**. Sending persons with an FASD out of the room to think about what they have done or responding to issues in a group session by simply ejecting them will often increase their sense of isolation and does not help them learn appropriate behaviors.
- **Do not blame people for what they cannot do**. Demanding that people repeatedly try to do things they cannot do is a lesson in frustration. It is important to have patience and understand individual limitations. People with an FASD may need something repeated several times because they have trouble remembering, not because they refuse to pay attention.
- **Set the person up to succeed**. Measures of success need to be different for different people. It is important to identify what would be a measure of success for the individual with an FASD and reinforce successes in concrete terms (e.g., "You did a great job of being on time for our session today. Thank you.") Training in social skills, anger management skills, and relaxation skills can help. In order for skills-building programs to be most successful for the person with an FASD, they need to be repeated periodically.

Resistance, Denial, and Acceptance
Individuals who have or may have an FASD may deny that they have a disability. Although some are relieved to know the cause of their difficulties, others may struggle to confront or accept their situation. The counselor needs to take time to help the person cope with the lack of understanding that often surrounds FASD. Women with an FASD, for instance, may fear becoming like their mothers and having a child with an FASD. An individual with an FASD may have difficulty with forgiveness of the birth mother, or may feel that it is inevitable that they will pass on FASD to their children. Counselors should reassure clients that they are not responsible for their disability, help them resolve their feelings about the birth mother, and educate them about the science of their condition (i.e., that it is not inevitable that they would pass on the condition). This process may take awhile, and the person may drift back and forth from accepting the disability to denying it. Exploring the reasons for the denial and understanding the client's fears can help.

Individual Counseling vs. Group Sessions
Individuals with an FASD may struggle to function in a group setting. Studies have shown increased levels of sensory sensitivities in this group, at least for children (Jirikowic et al., 2008). Clinical observations suggest individuals with an FASD can become overwhelmed by sensory input from large groups, noise, small spaces that cause crowding and touching of others, and visual distractions. Given the executive function deficits that are common in this clinical population, individuals with an FASD may not be able to process everything in the discussion and become lost. They may also 'talk too much,' and/or not be

able to effectively convey their feelings and ideas in group discussions.

Individual counseling may be needed to avoid some of the issues that arise in clients with an FASD who lack social skills and find group settings confusing or overwhelming. Talk therapy can be modified to incorporate role-playing, practice dialogues, play therapy, art therapy, and other methods that can draw on the strengths seen in individuals with an FASD. Printed material may be helpful, but should be written in simple language with a clear, non-distracting page layout.

If group work is necessary, the counselor can assist the client who has or may have an FASD by making some accommodations:

- Explain group expectations concretely and repeat these ideas often.
- If a person monopolizes conversation or interrupts, use a talking stick as a concrete visual reminder of who should be speaking. Hand the stick to the person whose turn it is to speak and pass the stick to others as appropriate.
- Give the person time to work through material concretely within the group time so he or she can ask questions or you can check understanding of material. The client may need extra time to process information. Listen for key themes to emerge slowly through the person's talk and behaviors.
- Allow the client to get up and walk around if he or she gets restless.
- Use concrete representations, such as marking the floor, to show the concept of boundaries.
- Make adaptations for the whole group to avoid singling out the client.

Use of a Mentor

Programs that work with individuals with an FASD have found that mentoring can be effective, as it provides a consistent, stable, one-to-one relationship and allows for the development of a personal bond with a trained individual who has knowledge and experience working with those who have an FASD (Malbin, 1993; Schmucker, 1997; Grant et al., 2004; Denys, Rasmussen, & Henneveld, 2011). A mentor can:

- Assist with the development of concrete and consistent rules and goals that will guide behaviors in specific situations;
- Improve comprehension in discussions with others (e.g., providers or other clients); and
- Assist with the development of personal scenarios for the adult to work out responses and practice through role-play.

Ongoing Assessment for Comprehension of Information

Extensive clinical observations reveal that individuals with an FASD may appear to understand when they do not. Parents often say their family member with an FASD "just doesn't get it." This means that individuals with an FASD may repeat information without actually understanding the content, and so will be unlikely to follow through. Because of this, it is important to provide consistency and re-check the retention of information often:

- Ask the client to summarize what you have said.
- Review written material, such as rules, at each session.
- Do not assume that the client is familiar with a concept or can apply it simply because you have reviewed it multiple times; have discussions that explore their understanding beyond simply being able to repeat the concept.

Clinical wisdom holds that the only consistent thing about FASD is that those who are affected behave inconsistently. This means, for example, that a client may demonstrate

that they know something on Monday, but have trouble recalling that same information on Tuesday. The clinician can benefit by following the rule to: REPEAT, REPEAT, REPEAT.

Sexual Abstinence, Contraception, and Pregnancy

Adolescents and adults with an FASD should be well informed and consulted about decisions regarding abstinence, contraception, and pregnancy. There are many ways to support pregnancy, delivery, and parenting by an individual with an FASD. The client may have questions about whether or not the FASD can be passed on to any offspring; caregivers must clarify that only prenatal exposure to alcohol can cause an FASD. If the client has children, the parenting skills taught to the client should account for the possible presence of an FASD in both parent and child; the skills learned must be appropriate to each of them and work for each of them.

Clinical experience reveals that women with an FASD can be vulnerable to exploitation and unintended pregnancy (Grant et al., 2004; Merrick, Merrick, Morad, & Kandel, 2006). It can be difficult for them to use contraception effectively due to memory lapses, problems following instructions, or difficulty negotiating contraceptive use with a partner. Counselors can help clients evaluate their family planning needs and assist in obtaining reliable, long-term birth control methods.

Although it may be unusual in a treatment setting, very practical and basic assistance may be important for a woman with an FASD. The counselor may need to accompany the client to a doctor's appointment to help her understand her options and choose the best one. One study found improved use of contraception among young women with an FASD by implementing a community intervention model of targeted education and collaboration with key service providers, and by using paraprofessional advocate case managers as facilitators (Grant et al., 2004).

Clinical consensus based on evaluation of common behavioral characteristics of FASD suggests that the causal relationship between HIV/STDs/viral hepatitis and substance use disorders may be heightened among those who also have an FASD. Care plans for individuals with an FASD entering substance abuse treatment should include communicable disease assessment.

Medication Assessment

In some cases, medication options may be appropriate to treat some of the functional or mental health components of FASD (Coe, Sidders, Riley, Waltermire, & Hagerman, 2001). The counselor may want to refer the client for an assessment to determine whether he or she can follow a regimen of taking a pill every day or getting a shot every few months. It is also important to consider the possible physical impact, since persons with an FASD may have health problems and be prone to side effects. Medications for individuals with an FASD may not work at rates similar to other populations and/or may require different dosages to work (O'Malley & Hagerman, 1999). Including a mentor or supportive family member in the discussion may help the individual with an FASD to be more comfortable asking questions and better understand what is being said.

Job Coaching

In a study of 90 adults with a diagnosed form of FASD, most had some work experience but the average duration was only 9 months (Streissguth et al., 1996). Some of the general barriers to successful work for people with disabilities are external; discrimination by employers, co-workers, and family, transportation issues, completing applications and job testing, social skills, and the lack of support

at interviews. Other barriers are internal, and need to be addressed early on in the vocational process; self-esteem and self-worth, fear of success, self-sabotage, and having a realistic view of strengths and career goals. All of these internal factors affect career choice, self-presentation at the interview and the job, and ultimate vocational success (Fabian, Ethridge, & Beveridge, 2009; Leon & Matthews, 2010). These issues should be addressed through counseling and skills-building prior to standard vocational tasks.

A job coach or vocational rehabilitation counselor may need to remain involved with an individual with an FASD beyond the time when he or she seems to "know" the job, and be understanding if the individual has days or situations in which he or she can't remember what to do or gets overwhelmed. Individuals with an FASD may do well enough on a job that a coach or counselor decides they "get it" and stops providing support, when in fact it was the support that enabled success.

Vocational Rehabilitation

Vocational Rehabilitation should be viewed as an interdisciplinary team process. It may be up to a parent or caregiver to coordinate information. The team may include a physician for medical and health issues, an occupational/physical therapist, a psychologist for counseling to address some of the above issues, teachers, case managers, and job placement agencies (Gobelet, Luthi, Al-Khodairy, & Chamberlain, 2007). Some adults and families will choose sheltered workshops because of concerns about safety, transportation, long-term placement, work hours, maintaining disability benefits, social environment, and work skills issues (Migliore, Grossi, Mank, & Rogan, 2008). At the same time, the majority of adults with an intellectual disability prefer integrated employment over sheltered workshops, regardless of disability severity (Migliore, Grossi, Mank, & Rogan, 2007).

Special Considerations for Adolescents Who Have or May Have an FASD

It is important to remember that adolescents are quite different from adults, and adolescents with an FASD differ from teens that develop in typical fashion. Adolescents with an FASD may function at social and emotional levels well below their chronological age, with an uneven cognitive and physical profile (some skills less impaired than others). The treatment process must incorporate the nuances of the adolescent's experience. In modifying treatment plans for adolescents with an FASD, it is important to consider cognitive, emotional, and social limitations, as well as risk factors that led to their substance abuse or mental health issue. Many youth with an FASD have grown up in less-than-ideal environments, facing parental substance abuse, economic deprivation, abuse, and multiple foster care placements. These situations can increase their risks for substance abuse and mental disorders.

A summary of clinical and empirical evidence shows that adolescents will commonly exhibit learning and behavior challenges, especially in adaptive function (getting along from day to day), and in remaining organized and regulated (Streissguth et al., 2004; Spohr, Willms, & Steinhausen, 2007). They often learn information slowly (especially what is said to them), tend to forget things they have recently learned, and make the same mistakes over and over. They can often have trouble shifting attention from one task to another. Like those with ADHD, they may be impulsive and find it hard to inhibit responses, and may be restless or even obviously hyperactive. In general, they may have trouble regulating their behavior. Even though adolescents with FASD may be talkative, they have social communication problems (such as leaving out important details or explaining things in a vague way). Adolescents with FASD tend to show poor judgment, are suggestible (and therefore easily

Treatment Tips From the Field

In addition to the guidance provided in this chapter, providers in British Columbia provided the following anecdotal suggestions for effective programming for individuals who have or may have an FASD.

Treatment Planning	• If medication is used, simplify medication schedules and provide support.
	• Avoid using students as therapists.
	  • May reinforce loss issues related to childhood/youth.
	  • May not be skilled with FASD.
	• Reassess concepts of dependency and enabling.
	• Use reminders.
	  • Use texting to provide reminders and stay connected.
	• Find something that the person likes to do and does well (that is safe and legal) and arrange to have the person do that regardless of behavior.
	• Create "chill-out" spaces in each setting.
	• Be creative about finding ways for the individual to succeed.
	  • Establish achievable, short-term goals.
	  • Reconsider zero-tolerance policies.
	• Be consistent in appointment days and times.
	  • Consider shorter, more frequent meetings or sessions.
	  • Arrange for someone to get the person to appointments for at least 6 months.
	  • Have the meetings on the same days each week.
	  • Discuss each meeting with the person.
	  • Use open meeting times, if necessary.

Assisting Navigation and Success	• Have pictures of the counselors on their office doors. • Identify possible buddies (e.g., family, friends, church or other organizations) to ensure the client gets to appointments, etc. • Identify persons who are appropriate supports for the client, as well as persons who are not helpful. • Program important numbers and reminders into their cell phone for them.

Language	• Do not use metaphors or similes.
	• Do not use idiomatic expressions and proverbs.
	  • "A day late and a dollar short."
	  • "People in glass houses shouldn't throw stones."
	• Don't use sarcasm, and be careful about joking with the person.

Source: Rutman, D. (2011). *Substance using women with FASD and FASD prevention: Service providers' perspectives on promising approaches in substance use treatment and care for women with FASD.* Victoria, British Columbia: University of Victoria.

influenced by others), and show immature social skills. Because of this, they may be too friendly with people they do not know well, too trusting, and have difficulty recognizing dangerous situations.

Treatment Plan Modification

It is generally believed that traditional forms of therapy, such as "talk therapy," are not the most effective choice when working with adolescents with an FASD. Their cognitive

Adolescent Development Issues in FASD

The following table outlines some of the more common developmental delays and deficits experienced by individuals with an FASD through the adolescent years (ages 12–21), and useful treatment approaches. This table is based on an expert clinical consensus.

Normal Development		FASD	Intervention
Age Range: 12-21	Ability to evaluate own behavior in relationship to the future	Lack of connection between thoughts, feelings, and actions	Repeated skills training with role-playing and videotaping; videotaping of person's behavior
	Understanding consequences of behavior		
	Importance of peer group	Difficulty resisting negative peer influences	Connect person with pro-social peers, mentors, and coaches
	Development of intimate relationships	Difficulty with accurately interpreting social cues (e.g., words, actions, nonverbal cues)	Social skills training; repeated discussions of sexuality and intimacy as appropriate

deficits prevent them from developing insight or applying lessons to their real lives. However, with creativity and flexibility, a treatment plan can be developed that includes techniques counselors are familiar with and comfortable with, adapted to fit the needs of the client (Baxter, 2000).

Addressing Peer Influences

Clinical observations indicate that adolescents with FASD are socially immature, and research documents that adults with FASD are more suggestible (Brown et al., 2011). Developmental literature makes clear that peer influences are important in the adolescent stage, and that deviant peer influences can lead to antisocial behavior. The counselor should address issues such as peer pressure in treatment to set the stage for less risky behavior outside treatment. Linking an adolescent with an FASD with a mentor is a sound treatment strategy.

Ongoing Assessment for Comprehension of Information

As with adults, it is important to check often to make sure the adolescent client understands what has been said. Ask the client to summarize what you have said. Review written material, such as rules, at each session. *Repeat, repeat, repeat*, even if the client says, "You've told me this a hundred times."

For adolescents, applying concepts can be difficult. Cognitive deficits, the frustration of having an FASD, and typical teen rebellion can make communication especially hard. Role-playing different situations, providing opportunities to share and process feelings, and giving the client time to process information is important. It also may help to use alternative methods of expression, such as drawing, to assist the client in sharing his or her understanding.

Educational Support (IDEA and FAPE)
The Individuals With Disabilities Education Act (IDEA) entitles every young person to a *f*ree and *a*ppropriate *p*ublic *e*ducation (FAPE) in the least restrictive environment. If the client is eligible, this can continue until age 21. If you have a client who has or may have an FASD and is in school, it is important to consult with the school regarding any provisions in that client's individualized education plan (IEP), either those identified by the school that should be carried over to treatment or vice versa. In a study of 120 children undergoing FASD diagnosis at a Washington State FAS DPN clinic, Jirikowic and colleagues (2010) found that over 90 percent did require intervention recommendations associated with their educational plan.

In the outpatient setting and during aftercare, it is a good idea for the psychologist to consult with the school counselor or case manager (if the client has one) regarding educational needs. Areas such as social skills may be addressed in the IEP, and are important to address during treatment and as part of aftercare. It also helps to be aware of any academic issues that may affect the client's treatment, such as stress about academic performance or difficulties with classmates.

Parents may not be aware of the laws regarding education of children with disabilities and may feel overwhelmed. They may be having problems dealing with their child's school and wonder what to do. The counselor can help by informing the client and family about IDEA and FAPE requirements and helping outline possible interventions to suggest to the school.

The U.S. Department of Education provides an online overview (**http://www2.ed.gov/about/offices/list/ocr/docs/edlite-FAPE504.html**) of the stipulations of FAPE and who qualifies for educational support under its terms.

In addition, vignette #10 in Part 1, Chapter 3 of this TIP discusses some of the key aspects of developing an IEP for an individual who has an FASD.

Psychosexual Development
Early and ongoing social experiences play a key role in psychosexual development. Adolescent tasks include having and maintaining intimate relationships, managing complex emotions and social situations, and developing independent thinking. The adolescent with an FASD may not achieve these milestones all at the same time, at the usual age range, or at all. Many adolescents with disabilities are delayed or prevented from achieving these goals by social isolation or a variety of functional limitations. Social skills may be broken down into manageable tasks, just as in every other area of instruction. This includes the basics first, such as mastering appropriate greetings, eye contact, body language, personal space, self-advocacy skills, and telephone and computer skills. A foundation in some or all of these basic skills will allow for the development of more complex skills. Mentors and peers may be very effective in this regard.

Vocational Coaching
Young adults with a disability need advocacy and support with a variety of new agencies and support services throughout the transition and adult years. A life skills curriculum should include how to use the internet to search for employment and employment enhancement services, awareness of issues associated with safe work environments, interviewing strategies, appropriate use of medication, managing finances, dealing with workplace routines and expectations, being cautious about at-risk situations, and knowing when to ask for help (Winn & Hay, 2009). Role-playing each of these skills with the client will be beneficial.

Counselor Self-Assessment

Working with clients with an FASD can raise issues for you, the counselor. You might feel resentment about being "stuck" with such challenging clients, or harbor negative attitudes toward women who drink while pregnant. The client with an FASD can trigger feelings of guilt and shame in a counselor who drank while pregnant or has a child with an FASD.

Understanding how to cope with clients with an FASD can help the counseling professional serve such clients more effectively. Olson and colleagues (2009) have underlined the importance of the need to **Reframe**, **Accommodate**, and **Have Hope** for caregivers raising those with FASD. These same strategies can help counselors, and are combined with the recommendations of Malbin (1993) and Schmucker (1997) to create the following recommendations for counselors providing FASD-related services.

REFRAME

Reframe your perception of the person's behavior. He or she is not trying to make you mad or cause trouble. He or she has brain damage and may have a history of abuse or other family dysfunction. You need to explore behaviors, stay patient, and tolerate ambiguity.

- Understand that FASD involves permanent brain changes.
- The client is not refusing to do things. He or she can't do them or does not understand what you are asking him or her to do.
- Clients often are not lying purposely. They are trying to fill in gaps in memory with their own information.
- Perseverating behaviors are an attempt to control or make sense of their own world.
- Transition and change are very difficult for the person with an FASD. Acting out when things change may be a reaction to fear of transitions or difficulty processing change.

ACCOMMODATE

- **Expect to repeat things many times in many ways**. Clients with an FASD may ask the same question every time you see them. Remember that these clients have cognitive deficits. They are not asking just to test your patience. Be patient and avoid looking bored going over the same information multiple times.
- **Use a written journal or goal sheets** to remind people how far they've come and where they are headed. Due to their memory difficulties, clients with an FASD will not always remember what supports or programs have been developed with them or their goals. Keep a positive attitude and focus on what the person has accomplished, rather than on goals yet to be met.
- **Realize that there is no set approach**; what works one time may not work the next. As part of the dysfunction of FASD, the client may experience things differently day to day or even hour to hour, and variability is the norm. Keep an open mind and be flexible. Avoid statements such as "But it worked last time."

HAVE HOPE

- **Be good to yourself**. Even with a realistic plan and an established routine, nothing is perfect. Things change and setbacks occur. By expecting bumps in the road of a person's journey through life, we can learn to not take these dips personally. By offering the person with an FASD nonjudgmental and informed support, we offer hope.
- **Know yourself**, and **take the time to reflect on your comfort level in dealing with issues surrounding FASD**. Gain knowledge if needed. Gain comfort in tackling the subject by role-playing with colleagues. Know your limits and get outside help or referrals as required. Plan to connect to appropriate community resources.

Thinking Ahead and Planning for the Future
It is important to think ahead and plan for the future with adolescents and young adults with FASD. If they are able to build an independent life, counselors can help the client learn how to self-advocate and self-monitor, and should communicate these skills to the client's caregivers, as well. It is important to think ahead about education on topics such as (1) safe sex; (2) communicating clearly with partners about consensual activity; (3) use of cigarettes and alcohol; (4) use of illicit substances, such as marijuana and drugs; (5) the consequences of criminal activity; and (6) ideas of what to safely do when the individuals goes through times of feeling irritable and negative (calming strategies).

5. Working with the Family

Introduction

Multiple studies have spoken to the value of involving the family in the treatment of an individual who has or may have an FASD, if possible (Schmucker, 1997; Grant, Ernst, Streissguth, & Porter, 1997; Olson et al., 2009; Olson, Rudo-Stern, & Gendler, 2011). Involving the family in planning, choosing, and shaping services for the client has become a key intervention concept in the field of developmental disabilities, as greater family involvement has been linked to better outcomes (Neely-Barnes, Graff, Marcenko, & Weber, 2008). Family-centered care is also strongly advocated for individuals with co-occurring mental health issues and a developmental disability like an FASD (McGinty, Worthington, & Dennison, 2008).

As with many clients in substance abuse and mental health settings, it is advisable to take a broad view of family. Many individuals with an FASD will have resided with foster parents and/or in kinship care (foster and adoptive scenarios being the most common), and care scenarios may extend well beyond the more typical ages of independence, like 18 or 21. Ultimately, who the client chooses to see as family or as the important caregiver in their life should be incorporated into the process, if possible.

As the table on the next page makes clear, involving the family can be as much about meeting their needs as the client's. The most frequently unmet family needs can be met with emotional support and, later in the counseling relationship, offering opportunities to "look forward" to the future and discuss both hopes and worries. Other frequently unmet needs can be met by helping caregivers find methods for self-care and respite. FASD education and appropriate intervention will meet other common needs, but may be less important (at the start) than support and direct assistance to help understand and meet caregivers' own needs.

Approaching the Family
It is imperative to obtain permission to approach family on the topic of an FASD. If the birth mother is still involved in the individual's care and is not aware of the possibility of an FASD, it is vitally important not to make her feel shamed or judged. The counselor should be prepared to address feelings of guilt. The family may also experience many of the feelings of anger, grief, and loss that the client experiences. All members of the family should be made to feel as comfortable as possible expressing these feelings.

If the family agrees to be involved, there are a number of ways that the counselor can support both them and the client. It is vital to use "reframing" to help the family better understand the client's behaviors as being at least partly caused by brain-based disabilities (Olson et al., 2009). A positive view of the affected individual, of the relationship between the caregiver and the individual, and of the caregiver process has been associated with

Top Unmet Needs for Caregivers Raising Children who have FASD and Behavior Problems

Percentage Indicating Need is Unmet	Type of Family Need
69.2%	Discuss feelings about my child with someone who has gone through the same experience.
61.7%	Have help in preparing for the worst.
60.8%	Have enough resources for myself or the family.
58.8%	Have help in remaining hopeful about my child's future.
58.0%	Get a break from my problems and responsibilities.
55.8%	Be reassured that it is usual to have negative feelings about changes in my child's behavior.
52.9%	Have complete information on my child's thinking problems.
51.0%	Be shown what to do when my child is upset or acting strange.
48.1%	Be told why my child acts in ways that are different, difficult or strange.
47.1%	Have different professionals agree on the best way to help my child.
47.1%	Pay attention to my own needs.

'Important' is defined as parent report that a need was 'important' or 'very important' (where there were two other levels indicating less importance). 'Unmet' was defined as parent report that a need was met 'not at all' or 'a little' (where there were two other levels indicating that a need was met more completely). Items shown here were the most frequently endorsed items; the remaining items (of 20) received far less frequent endorsements.

Source: Olson, H. C., Oti, R., Gelo, J., & Beck, S. (2009). "Family Matters:" Fetal Alcohol Spectrum Disorders and the family. *Developmental Disabilities Research Reviews, 15*, 235-249.

more positive outcomes for the individual and family (Blacher & Baker, 2007). The counselor can then help the family reach out to extended family and friends to help them reframe the situation. Reframing can help everyone more positively understand the client's behavior, and appropriately adjust the home and school environments. Treatment approaches that stress problem-focused management and stress reduction may be a useful addition to parent training (Olson et al., 2009). Other suggestions include:

- As with the client, review the diagnostic report thoroughly with the family (if it is available). Chapter 3 of Part 1, *Clinical Vignettes*, contains a vignette illustrating this process.
- Help the family arrange for respite care or a community support worker: Caregivers may feel stressed or burned out by the responsibilities of caring for someone with an FASD.
- Assist family in coming up with ways to educate extended family and friends about FASD to help them understand the client's behaviors and adjust the home environment accordingly.
- Connect family and friends with support groups or other community resources (see Step 6).
- Help find long-term mentors for clients. Family members or friends who have become exhausted or burned out dealing with an FASD may be willing to help

after a mentor has stepped in for awhile and the client has made progress.

- Encourage parents and caregivers to maximize independence, even if they are used to "helping" or completing tasks for the client.
- Help the family access needed services and supports (see Appendix G, *Services and Supports Checklist*, for a list that can be used as a worksheet).

The *Families Moving Forward Program* intervention is a scientifically-validated behavioral consultation program tailored for families raising preschool and school-aged individuals with FASD or confirmed prenatal alcohol exposure. The intervention includes methods and materials that appropriately trained counselors can use when working with families of a client who has an FASD, even if the client is older (**http://depts.washington.edu/fmffasd**). See Appendix F, *Sample Crisis/Safety Plan*, and Appendix G, *Services and Supports Checklist*, for materials that have been adapted from the *Families Moving Forward Program* for this TIP.

If the client had an existing diagnosis of an FASD before presenting in your setting, involving the family is still valuable. Caregivers are probably already well-versed in FASD and the difficulties of obtaining effective services, and can be as much of a resource of information for the counselor as the counselor is for the family.

6. Transition and Connection to Community Supports

Transitional Services

Part of the counselor's role is to prepare for discharge of the client. This involves working to establish a network of community resources and providers of service who will continue to provide support and advocacy when your role is complete. Providing these supports with education about FASD and the client's unique patterns of behavior is an important part of successful transitioning. See Appendix G, *Services and Supports Checklist*, for a worksheet that can be used to quickly identify linkages the counselor and client may want to explore.

Network of Providers

Counselors need to be familiar with available resources in the community, such as psychiatrists, social workers, developmental disability providers, and physicians. Counselors can include referrals to these resources in the transition plan and work with case managers at their facility as appropriate. For clients who are still in school, it is also important to consider the transition to school, and to work with school administrators and/or the school counselor to determine how best to address the client's ongoing needs within the school setting.

It may also be necessary to consult an advocate or legal representative if the client has had any legal problems. Adolescents with an FASD can get pulled into illegal activity or manipulated into relapses.

Mentorship

Locating a long-term mentor within the person's sphere of relationships can be another way to support the transition process. Providing tips and strategies for things that have worked well with the client during treatment can enable the mentor to provide support in the future (Schmucker, 1997). There are also organized programs that can help to identify mentors, though these resources are scarce and differ by community.

If the family is involved in treatment and the client had an existing diagnosis of an FASD before treatment, it is likely that they will have developed relationships with a variety of providers and can thus potentially be a useful

resource for information on services available in the community. There are a number of things that should happen during transition planning that a parent or caregiver could help to facilitate, such as introduction to the relevant service providers and transfer of information to those agencies.

Assessment of Living Skills/Planning for Safety

Even if taught as part of treatment, basic functional living and social skills will need to be re-assessed before transition to help the client function more effectively and safely in the community. The provider should work with the client to:

- Assess ability to handle money, pay bills and rent, buy groceries, etc. The clinician can consider a representative payee, if necessary.
- Anticipate housing needs: Will the client live alone? With caregivers? With others in structured housing or a group setting? An individual with an FASD is likely to need dedicated, long-term caregiver support in any setting, but this is particularly vital if they will be living alone. Assistance is likely to be needed with negotiating public transportation, handling interpersonal relationships, grocery shopping, and structuring leisure time (Streissguth et al., 1996).
- Identify job desires and possibilities, as well as what is needed for job success.
- Review appropriate social interaction.
- Review processes for checking whenever the client is unsure of a situation or response, or is in trouble.
- Ensure that learned skills are practiced in the new environment.
- Continue supports at least until the client adjusts to the new environment.

If a mentor, family member, or other caregiver is identified for the client, Vignette #9 in Part 1, Chapter 3 of this TIP walks through the process of working with that person or persons to develop a personalized Safety Plan on behalf of an individual with an FASD.

Connection to Community Supports

Both the client and the client's family and caregivers (if involved) can benefit from connection to support systems in their community. As with referral for assessment or diagnosis, it is vital that the counselor actively assist the client through transition to other providers and follow up regularly to ensure client satisfaction and full and open communication between agencies and with the client (and the client's family, if they are involved in the treatment process).

Appendix C, *Public and Professional Resources on FASD*, provides links to a number of support organizations for individuals with an FASD, including NOFAS (**www.nofas.org**), the Birth Mothers Network (also known as the Circle of Hope; visit the NOFAS Web site and the FAS Community Resource Center (**http://www.come-over.to/FASCRC/**).

NOFAS can be a particularly valuable resource, as it houses not only the Birth Mothers Network but also an extensive affiliate network whose members provide a broad range of FASD-related services to individuals and their families. In addition, NOFAS's "Living With FASD" page (**http://www.nofas.org/living/**) contains links to financial assistance programs such as Supplemental Security Income (SSI), Social Security Disability Insurance (SSDI), and Medicaid, as well as family and mother support programs such as Women, Infants and Children (WIC).

An emerging community resource for individuals with an FASD is the Self-Advocates with FASD in Action (SAFA) Network. Members

include individuals with an FASD and their support persons. The SAFA Network provides speakers and training on living with an FASD, and also peer support for other individuals and families coping with these disorders. The SAFA Network can be contacted through SAMHSA's FASD Center for Excellence (**www.fasdcenter.samhsa.gov**, or toll-free at 1-866-STOP-FAS).

Job Support

Your local One-Stop Center (**www.careeronestop.org**) may provide links to your state Department of Labor and Workforce Development, the local division for vocational rehabilitation services, and/or specific state initiatives for development of customized employment for people with disabilities. For individuals with an FASD, customized employment should include a protocol that addresses their special needs.

Self-Help Participation

The person with an FASD will need support to participate successfully in a 12-Step program. Many areas of the country have "Double Trouble" meetings; these are 12-Step self-help groups designed to meet the special needs of people with addiction and mental health issues (Vogel, Knight, Lauded, & Maura, 1998). Double Trouble meetings may be more flexible about impulsive behaviors than routine meetings. The counselor should be cautious about referring a client who has or may have an FASD into a self-help group, due to issues of victimization as well as the possibility that the individual's special needs will not be met.

Another significant resource for people with an FASD and co-occurring issues is the recovery movement in the mental health field. Recovery centers (also known as "drop-in" centers) offer a variety of supports, groups, and meetings in some areas.

For more information on treatment approaches with individuals who have or may have an FASD...

Vignettes 5–10 in Part 1, Chapter 3 of this TIP illustrate scenarios where a counselor works with a client who has or may have an FASD, or provides assistance to family members/caregivers. In addition, Part 3, the online Literature Review, also contains further discussion of interventions, protective factors, and co-occurring issues.

3 Clinical Vignettes

IN THIS CHAPTER

Introduction

This chapter presents vignettes of counseling/intervention sessions between various service professionals and either 1) women of childbearing age where FASD prevention is warranted, and/or 2) individuals who have or may have an FASD or their family members. The vignettes are intended to provide real-world examples and overviews of approaches best suited (and not suited to) FASD prevention and intervention.

The Culturally Competent Counselor

This TIP, like all others in the TIP series, recognizes the importance of delivering culturally competent care. Cultural competency, as defined by HHS, is…

"A set of values, behaviors, attitudes, and practices within a system, organization, program, or among individuals that enables people to work effectively across cultures. It refers to the ability to honor and respect the beliefs, language, interpersonal styles, and behaviors of individuals and families receiving services, as well as staff who are providing such services. Cultural competence is a dynamic, ongoing, developmental process that requires a long-term commitment and is achieved over time" (U.S. Department of Health and Human Services, 2003, p. 12).

A critical element of this definition is the connection between attitude and behavior, as shown in the table on the next page.

Areas of Clinical Focus

In this chapter, you are invited to consider different methods and approaches to practicing prevention of an AEP and/or interventions and modifications for individuals who have or may have an FASD. The ten scenarios are common situations for behavioral health professionals and focus on:

Attitude	Behavior
Respect	• Acknowledging and validating the client's opinions and worldview • Approaching the client as a partner in treatment • Communicating with clients in their primary language, either directly or through an interpreter • Respecting the client's self-determination
Acceptance	• Maintaining a nonjudgmental attitude toward the client • Considering what is important to the client
Sensitivity	• Understanding the client's experiences of racism, stereotyping, racial profiling, and discrimination • Understanding the life circumstances, daily realities, and financial constraints of the client
Commitment to Equity	• Intervening on behalf of clients when a problem stems from racism or bias • Actively involving oneself with minority individuals outside the counseling setting to foster a perspective that is more than academic or work-related
Openness	• Recognizing the value of indigenous helping practices and intrinsic help giving networks in minority communities • Building ongoing collaborative alliances with indigenous caregivers • Seeking consultation with traditional healers and religious and spiritual leaders and practitioners in treatment of culturally different clients, when appropriate
Humility	• Acknowledging the limits of one's competencies and expertise and a willingness to refer clients to a more appropriate counselor when necessary • Seeking consultation and pursuing further training or education, or a combination of these • Constantly seeking to understand oneself as being influenced by ethnicity and culture and actively seeking a nonracist identity • Being sensitive to the power differentials between the client and the counselor
Flexibility	• Using a variety of verbal and nonverbal responses, approaches, or styles to suit the cultural context of the client • Using cultural, socioeconomic, and political contextual factors in conducting evaluations and providing interventions

This table originally appeared in TIP 48, *Managing Depressive Symptoms in Substance Abuse Clients During Early Recovery* ((SMA) 08-4353). The authors of this TIP gratefully acknowledge the authors of TIP 48.

1. Intervention with a woman of childbearing age who has depression, is consuming alcohol, and may become pregnant (AEP Prevention)
2. Examining alcohol history with a woman of childbearing age in substance abuse treatment for a drug other than alcohol (AEP Prevention)
3. Intervention with a woman who is pregnant (AEP Prevention)
4. Intervention with a woman who is pregnant and consuming alcohol, and who is exhibiting certain triggers for alcohol consumption, including her partner (AEP Prevention)
5. Interviewing a client for the possible presence of an FASD (FASD Intervention)

6. Interviewing a birth mother about a son who may have an FASD and is having trouble in school (FASD Intervention)
7. Reviewing an FASD diagnostic report with the family (FASD Intervention)
8. Making modifications to treatment for an individual with an FASD (FASD Intervention)
9. Working with an adoptive parent to create a safety plan for an adult male with an FASD who is seeking living independence (FASD Intervention)
10. Working with a birth mother to develop strategies for communicating with a school about an Individualized Education Plan for her daughter, who has an FASD (FASD Intervention)

Organization of the Vignettes

To better organize the learning experience, each vignette contains an **Overview** of the general learning intent of the vignette, **Background** on the client and the setting, **Learning Objectives**, and **Master Clinician Notes** from an "experienced counselor or supervisor" about the strategies used, possible alternative techniques, timing of interventions, and areas for improvement. The Master Clinician is meant to represent the combined experience and expertise of the TIP's consensus panel members, providing insights into each case and suggesting possible approaches. It should be kept in mind, however, that some techniques suggested in these vignettes may not be appropriate for use by all clinicians, depending on that professional's level of training, certification, and licensure. It is the responsibility of the counselor to determine what services he or she can legally/ethically provide.

1. INTERVENTION WITH A WOMAN OF CHILDBEARING AGE WHO HAS DEPRESSION, IS CONSUMING ALCOHOL, AND MAY BECOME PREGANT (AEP PREVENTION)

Overview: This vignette illustrates how and why a counselor would address prevention of an AEP with a young woman who is being seen for depression.

Background: This vignette takes place in a college counseling center where Serena, 20, is receiving outpatient services for the depression that she's been feeling for about 4 months. In her intake interview, Serena has indicated that she consumes alcohol, is not pregnant, and is sexually active. She has had two prior sessions with the counselor, during which they have discussed Serena's general background, family interactions, social supports, and her outlook on school.

In today's session, they have been discussing her boyfriend, Rob. A therapeutic relationship has begun to form between Serena and the counselor, and the counselor would now like to explore Serena's alcohol use and whether it is a possible contributing factor in her depression. While doing this, the counselor will identify an opportunity to deliver an informal selective intervention to prevent a possible AEP.

Learning Objectives:

1. To illustrate that clients often have multiple issues that need to be addressed besides their primary reason for seeking counseling.
2. To demonstrate a selective intervention ("FLO") for preventing an alcohol-exposed unplanned pregnancy.
3. To recognize that prevention of an AEP can be accomplished by eliminating alcohol use during pregnancy or preventing a pregnancy during alcohol use; often the most effective route is to prevent the pregnancy.

Vignette Start

The session is already in progress. Serena has been discussing how she and her boyfriend Rob tend to fight a lot, but she continues to spend time with him because they have fun at parties.

COUNSELOR: So, how long have you and Rob been together?

SERENA: About 7 months.

COUNSELOR: And you've said that the two of you are sexually active.

SERENA: Yeah, I usually sleep over on the weekend, after the parties.

COUNSELOR: Do these fights occur at any particular time?

SERENA: Not really. When we're stressed, mostly, over school or work or whatever. Then I feel more depressed cuz we're fighting, and he gets upset because I'm depressed. It's like a circle. That's why we go to the parties, to unwind and forget about stuff.

COUNSELOR: And then you tend to end up spending the night with him.

SERENA: Usually.

COUNSELOR: Are you using any protection, or birth control?

SERENA: No.

COUNSELOR: And during these parties, are you drinking?

SERENA: Sure.

COUNSELOR: About how many drinks do you have?

SERENA: I don't really know. My cup's never empty, it just gets refilled at the keg.

COUNSELOR: Are there other times when you drink alcohol?

SERENA: No, it's really just at the parties.

Master Clinician Note: Serena is presenting high-risk behavior by combining alcohol use and unprotected sex. The counselor seeks to identify the link between alcohol, unprotected sex, and pregnancy.

COUNSELOR: I know you're not expecting this, but if you were to find out right now that you were pregnant, how would that change things for you?

SERENA: Oh lord, that would *totally* turn my life upside down. And Rob's. God, he'd freak.

COUNSELOR: So, you do *not* want to get pregnant.

SERENA: No, I definitely do not wanna get pregnant.

Master Clinician Note: Serena has made it clear that she does not want to become pregnant, so the counselor shifts to addressing the gap between Serena's behaviors (being sexually active but not practicing safe sex) and her stated desire (to not get pregnant).

COUNSELOR: I understand, and I'm concerned about your health and what you want for your future. So, if you plan to keep attending these parties and being sexually active, then maybe we can talk about contraception. Did you know that half of all pregnancies in the U.S. are unplanned?

SERENA: Wow. No, I didn't know that.

COUNSELOR: It's true. It's possible that you could get pregnant, and the drinking could impact the health of that baby. Let's talk about how we can avoid those things.

SERENA: Okay.

The counselor gives Serena a pamphlet that describes effective contraception.

COUNSELOR: Would you be willing to read this? It's short, but it has good information. Perhaps we can go over it when we meet next week.

SERENA: Okay. I thought I was here to talk about depression, though.

COUNSELOR: Yes, absolutely, our first goal is to help you stop feeling depressed. And as you've said, you definitely don't want to have a baby, so I think it's important for us to discuss ways to avoid getting pregnant, so that that's not something that adds to your worries.

SERENA: Oh, okay. I see what you mean.

COUNSELOR: So next week I can answer any questions you have about that material, and then we can talk about some positive goals you want to lay out, like feeling less depressed, or fighting with Rob less, or not getting pregnant. Does that sound okay?

SERENA: Yeah, thanks.

Master Clinician Note: This vignette does not "solve" the issue of Serena's depression. However, as part of examining the possible causes, Serena has talked about a pattern of regular at-risk drinking, combined with unprotected sex. Because of this, the counselor—who by now has established a good rapport with Serena—has taken the opportunity to carefully include a selective intervention for preventing an AEP.

In an informal way, the counselor has used the steps of the "FLO" intervention discussed in Part 1, Chapter 1 of this TIP. During intake and again at this visit, Serena has indicated that she consumes alcohol and is sexually active. The counselor provides **F**eedback on these responses (by discussing the possibility of an AEP), then **L**istens as Serena indicates that she does not want to become pregnant. The counselor thus shifts the focus of medical advice to the **O**ption of contraception and provides Serena with educational material.

At the same time, the counselor has not lost sight of depression as Serena's primary treatment issue. In this session, the counselor has laid the groundwork for continuing to discuss Serena's at-risk drinking and her problematic relationship with Rob as possible components of the depression, but in the context of positive goals that Serena can aim for (i.e., finding ways to feel less depressed, fight with Rob less, and avoid an unwanted pregnancy).

2. EXAMINING THE ALCOHOL HISTORY WITH A WOMAN OF CHILDBEARING AGE IN SUBSTANCE ABUSE TREATMENT FOR A DRUG OTHER THAN ALCOHOL (AEP PREVENTION)

Overview: This vignette illustrates the value of asking about alcohol use in a female substance abuse treatment client of childbearing age, even though her primary drug is not alcohol.

Background: Chloe is being seen at an outpatient treatment center for methamphetamine abuse. The counselor has the health history that was provided during intake. It indicates that Chloe reports as non-pregnant, but is 28 (of childbearing age) and is sexually active.

The counselor wants to explore whether Chloe is using other substances, as well as screening for a possible mental health problem. Given that the client is sexually active, there is a risk of an unplanned pregnancy, therefore the counselor begins with alcohol.

Learning Objectives:

1. To emphasize the importance of probing for alcohol use even if it is not the primary drug.
2. To recognize that quantity of use is subjective. The use of a visual helps the client understand what a one-drink equivalent is.
3. To recognize that if a mental health issue presents itself, it will need to be addressed concurrently.

Vignette Start

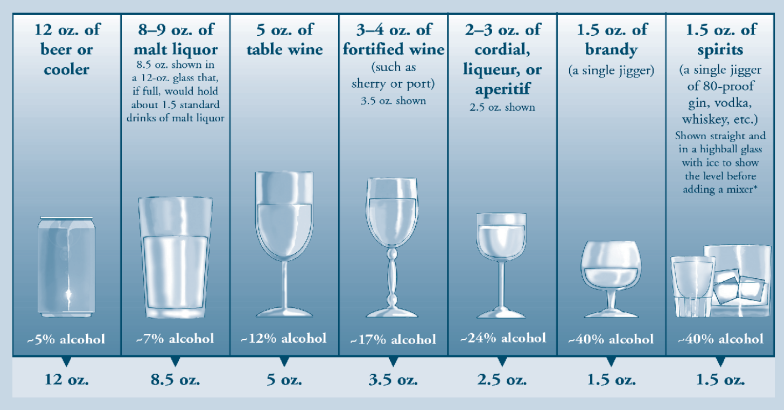
COUNSELOR:	Hi, Chloe.
CHLOE:	Hey.
COUNSELOR:	Please have a seat. I have some questions that I would like to ask you, Chloe. You're in treatment for methamphetamines, correct?
CHLOE:	Yes.
COUNSELOR:	If it is okay with you, I would like to ask you first about your use of some other drugs. I would like to start with alcohol. Do you know how much alcohol you drink?
CHLOE:	You mean, altogether? I don't know.
COUNSELOR:	Okay, in an average week, how much alcohol would you say you drink?
CHLOE:	Well, usually I just drink enough to wash down my pills.
COUNSELOR:	What pills are those?
CHLOE:	The, whatayacallit, desoxyn.
COUNSELOR:	And what do you wash these pills down with? What kind of alcohol?
CHLOE:	Usually vodka. With some orange juice in it.
COUNSELOR:	And do you do this every time you take the pills?
CHLOE:	Not every time, but most times.

COUNSELOR: Okay. And how much vodka do you drink to wash down the pills?

CHLOE: One drink.

COUNSELOR: Here, let me show you something real quick. This is a picture of different glasses that people tend to use for drinking alcohol. Which one do you use?

Master Clinician Note: The counselor uses the visual below to help Chloe more concretely understand her level of consumption. However, this visual does not reflect every available drinking size or container, so any discussion of a standard drink should incorporate the client's personal experience (i.e., "If you don't see your glass on here, what do you use?").



CHLOE: None of them. Well (*Chloe indicates the 8.5 ounce drinking glass*), that looks like what I use, but it's not all vodka.

COUNSELOR: How much do you fill with vodka, and how much orange juice?

CHLOE: About half and half.

COUNSELOR: All the way to the top?

CHLOE: Yeah, but with ice in it.

COUNSELOR: Okay, so that's going to be about three to four ounces of vodka, and an ounce and a half of hard liquor is equal to one drink. So, it looks like you're having the equivalent of two to three drinks every time you wash down the pills.

CHLOE: Hmm. I didn't know that.

COUNSELOR: Is there any other time when you use alcohol?

CHLOE: I may have some when I'm feeling bad. It takes the edge off.

COUNSELOR: Can you tell me more about how you feel when you "need to take the edge off?"

CHLOE: I just feel very upset, worried. Sometimes sad.

COUNSELOR: That must be hard for you. About how often do you feel worried and/or sad?

Master Clinician Note: The counselor expresses empathy for the client and how sad/worried she is feeling. This expression of empathy assists in establishing more of a caring relationship, so that further questions around alcohol use can be explored in a helpful manner. The counselor also explores more with the client about how she is feeling when she talks about "taking the edge off" to see what might be the result of her drug use and to see if she needs a mental health evaluation. A mental health evaluation might explore whether medication is indicated that could assist Chloe in reducing her alcohol use.

CHLOE (*laughs*): A lot.

COUNSELOR: It must be difficult to feel so sad and worried a lot. Can I ask you a few more questions about this?

CHLOE: Okay.

COUNSELOR: Did you feel very sad or worried this week?

CHLOE: Yeah.

COUNSELOR: So, when you felt this way this week, did you need to use alcohol to feel better? Or, as you said, to take the edge off?

CHLOE: (*shrugs*) Yeah, I had three or four drinks.

Master Clinician Note: The counselor does not assume that the client is deliberately underestimating, but keeps in mind that clients may minimize when self-reporting alcohol use (Taylor et al., 2009).

COUNSELOR: Did you also feel like this *last* week?

CHLOE: Probably.

COUNSELOR: How about last month? Did you need to use alcohol to try to feel better then also? That would have been August.

CHLOE: I'm sure I did.

COUNSELOR: So Chloe, you would say that you're feeling sad and worried, and using alcohol to help you feel better, has been going on for quite a while, is that right?

CHLOE: Yeah, most of this year.

Master Clinician Note: Given the frequency of poly-drug use among clients in substance abuse treatment, this counselor did not assume that methamphetamine was the only substance that Chloe was using. Through some simple probing, the counselor has identified that not only has Chloe been drinking, she has been doing so at a high-risk rate. At a future time when dealing more specifically with the amount Chloe is drinking, the counselor might show her a chart with drinking frequencies to help Chloe see what level of drinking is defined as heavy and/or problematic for women.

Chloe has also talked about a pattern of self-medication. The reason or trigger for this may be depression; Chloe has said only that she drinks when she is "feeling like s&@*." This will require further exploration. For now, the counselor knows that a potential co-occurring mental health issue, a co-occurring substance abuse issue, and prevention of a possible AEP should all be factored into the treatment plan.

3. INTERVENTION WITH A WOMAN WHO IS PREGNANT (AEP PREVENTION)

Overview: This vignette illustrates that screening for alcohol use should be done at every visit with women who are—or are at an indicated likelihood for becoming—pregnant. Alcohol-exposed pregnancies occur in all demographics, regardless of socio-economic status, age, ethnicity, or marital status.

Background: April, 27, works full-time. She recently found out she is pregnant with her first child. She and her husband have relocated to a new city, and she is being seen at a private OBGYN office for the first time.

Learning Objectives:

1. To recognize that asking about alcohol use during the first visit only is not enough; screening should occur at every visit.
2. To identify that a woman could begin drinking during the pregnancy if she is experiencing a relapse.
3. To highlight there is no known safe amount of alcohol use during pregnancy.

Vignette Start

1st Office Visit

PRACTITIONER: Hello, I'm Dr. Johnson. I see on the chart that you are pregnant. Congratulations!

APRIL: Thank you.

PRACTITIONER: I have a number of questions that I need to ask you before the exam.

Practitioner inquires about health history and eating habits, recommending an increase in fruit consumption.

PRACTITIONER: A few other quick questions. How much do you smoke per day?

APRIL: I don't smoke.

PRACTITIONER: That's good! How much coffee and water do you drink?

APRIL: I have a cup of coffee in the morning, that's about it. I try to drink water all the time. I don't know how much I have per day. Probably a few glasses worth.

PRACTITIONER: Okay, how often do you drink alcohol?

Master Clinician Note: The practitioner has included alcohol as part of a general health exploration rather than asking the question by itself, which can make some clients nervous. Still, April looks a little concerned.

APRIL: I don't drink any alcohol.

PRACTITIONER: Okay, that's good to hear. Not to worry, that's just a general question that I will be asking during all of our visits. There's no safe time, amount, or kind of alcohol to drink during pregnancy, so we recommend women not drink during their pregnancy.

2nd Office Visit: *We pick up the conversation after the practitioner has again gone over the general health questions about smoking and level of intake of water and coffee.*

APRIL: I'm actually trying to drink more water now, and less coffee. I carry a water bottle around with me all the time.

PRACTITIONER: Okay, that's good. How much alcohol have you had?

APRIL: None, really.

PRACTITIONER: Have you had *any* alcohol?

APRIL: One glass. We were having dinner with some friends.

Master Clinician Note: This interaction demonstrates the value of re-screening in relation to alcohol. April stated in the first visit that she does not drink. However, during this second visit, she has revealed that she does drink on occasion. It will be important for the practitioner to repeat the benefits of abstinence during pregnancy and probe for level of alcohol use, while remaining supportive and nonjudgmental.

PRACTITIONER: I see. Well, as we discussed at your last visit, no alcohol use during the pregnancy is the best policy. We just want to take the best possible care of your baby. About what size was that glass, would you say?

Master Clinician Note: The practitioner can use a visual aid, as in the previous vignette, to help April understand how much really equals one drink. The practitioner has also repeated the importance of abstinence during the pregnancy, and tied the guideline specifically to the health of April's baby.

3rd Office Visit: *At this visit, April again indicates alcohol consumption, this time "a couple of drinks" at a dinner party. The practitioner explores further.*

PRACTITIONER: How many drinks did you have?

APRIL: Well, my friend handed me a glass of cabernet when I arrived, because she said I would love it. I reminded her that I was pregnant, but she said a couple wouldn't hurt and that she had a few when she was pregnant and her kids were fine.

PRACTITIONER: So, you drank the cabernet. Did you have any others?

APRIL: Well, then I had some with dinner, too. I felt like I had been really good during the pregnancy, so I just decided to have a few drinks this one night.

PRACTITIONER: So, you ended up having a few drinks that night.

APRIL: Yes, but just that one time. And it was only wine.

PRACTITIONER: I know that the temptation to have some drinks at a party or a celebration can be great, but there are a couple things to keep in mind. One is that science has shown that alcohol can harm the baby. We don't know yet how much alcohol consumption is too much, so it's very important to avoid all alcohol during the pregnancy.

The practitioner pauses for the client to process what has been said.

APRIL: Okay.

PRACTITIONER: Also, it's important to understand that *any type* of alcohol you drink can hurt the baby, not just certain kinds. Wine, hard liquor, beer…any beverage with alcohol in it. So it's important to avoid all of them during the pregnancy.

APRIL: Gotcha.

Master Clinician Note: Given that April has continued to drink even after her first couple of visits, the practitioner takes the educational process a step further this time, clearly noting that science has established a risk and that there is no "acceptable" form or amount of alcohol. A counselor or practitioner may also want to discuss the possibility of equipping April with some tools to help her abstain during the pregnancy (e.g., relaxation techniques, recreation, avoiding trigger situations such as parties). The need to continue to monitor April's alcohol consumption should be clearly noted in the medical record.

4. INTERVENTION WITH A WOMAN WHO IS PREGNANT AND CONSUMING ALCOHOL, AND WHO IS EXHIBITING CERTAIN TRIGGERS FOR ALCOHOL CONSUMPTION, INCLUDING HER PARTNER (AEP PREVENTION)

Overview: This vignette illustrates a method for obtaining the alcohol history of a pregnant woman.

Background: Isabel, 30, has been referred to an outpatient mental health treatment center for feelings of depression. She is Hispanic, married, and pregnant (in her third trimester), and has one other child. The counselor and client have completed the intake process and Isabel has participated in the development of her comprehensive treatment plan. This is their third meeting. The counselor and Isabel agreed at the end of their last session that this would be about potential health risks with the pregnancy.

Learning Objectives:

1. To learn how to use a practical visual tool (a calendar) to more accurately and effectively identify client drinking patterns and possible triggers for alcohol consumption.
2. To identify verbal cues that can indicate that a topic is becoming uncomfortable for a client, and apply effective techniques when a client becomes upset.

Vignette Start

COUNSELOR: Hi, Isabel. How are you?

ISABEL: Fine, how you doing?

COUNSELOR: I'm fine, thanks. When we met last, we finished working on your treatment plan. You have had a little bit of time to think about the plan now. Do you have any thoughts or concerns about what we developed?

ISABEL: No, not really.

COUNSELOR: How are you doing with the pregnancy?

ISABEL: Pretty good. Things are going pretty well.

COUNSELOR: Great. Now, at the end of your last visit here, we said we would spend part of today's session talking about alcohol use during pregnancy. You indicated during your intake that you drink socially, so let's talk about that a little more. Knowing about when and how much you drink will help us to see if there is any need to be concerned about any health issues for you or the baby. Is that okay with you?

ISABEL: *[Sounding a little concerned.]* What do you mean "concerned about health issues?" I am not an alcoholic.

Master Clinician Note: The counselor wants to reassure Isabel that she has not formed a negative opinion of her. The counselor now also needs to be aware that Isabel may try to minimize the frequency and amount of alcohol consumed so that she is not viewed as an alcoholic.

COUNSELOR: *[Calmly and reassuringly.]* I am sorry, Isabel. I wasn't trying to say that you have an alcohol problem. Nothing you have told me during our previous sessions would lead me to believe that you are an alcoholic or have a drinking problem. You said you only drink socially, correct?

ISABEL: Yes. I don't drink every day or even every weekend.

COUNSELOR: Good. That's just what I thought. I know, just from the short time we have been seeing each other, that you would never do anything to hurt your child. But, would you agree that drinking socially for one person might be different than drinking socially for another?

ISABEL Of course.

COUNSELOR: Alcohol can have an influence on individuals who are anxious, depressed, and even on women who are pregnant, and possibly their unborn child. That influence can depend on the frequency and amount of alcohol consumed. So knowing the social situations and how much you drink at those occasions will help us determine if you need to make any changes between now and when the baby is born. If it is okay with you, let's see if we can identify those situations.

ISABEL: Okay, I'll give it a try.

COUNSELOR: Thanks. That's great. So first let me ask you this: Normally, when you aren't pregnant, how often would you say you drink alcohol?

ISABEL: Well, most of the time I'm not normally a drinker.

COUNSELOR: Okay, that's good. When you *do* drink, about how much do you have?

ISABEL: I can't really say. It depends.

Master Clinician Note: The counselor wants to get an accurate picture of Isabel's drinking during pregnancy, so she brings out a calendar. The visual is helpful as it allows both client and counselor to put their eye contact elsewhere, which can contribute to the ease of discussion. The counselor explains that it also helps to trigger memory by looking at dates.

COUNSELOR: Okay, so let's start by figuring out when you first found out that you were pregnant.

ISABEL: I went to Dr. Murphy's office and they did a pregnancy test. I had not had my period. I can look at the calendar, but I am pretty sure it was sometime in May.

COUNSELOR: Do you think it was the beginning of May or the middle?

ISABEL: It was the middle, and then I went home and told Marco.

COUNSELOR: Ok, so you found out you were pregnant in the middle of May. *[Counselor marks the calendar.]* When did Dr. Murphy tell you your due date would be?

ISABEL: Around December 22.

COUNSELOR: Great, so we know you're in your third trimester now. *[The counselor circles the third trimester with a colored pencil, then circles the other trimesters with different colors.]* It looks like you probably got pregnant somewhere around the beginning of April. *[The counselor also marks this on calendar.]* Did your alcohol drinking change after you found out you were pregnant in mid-May?

ISABEL: Yes, I pretty much quit drinking after that. But right before, around the beginning of May *[points to calendar]*, Marco had just gotten a job and we went out with some friends. We went to party that one time, and I drank a little, but I don't think that would harm the baby. It wasn't a lot.

COUNSELOR: You're doing great. Do you remember what you were drinking?

ISABEL: I had one rum and Coke. Mostly Coke, with a little rum.

COUNSELOR: Was that all?

ISABEL: I had one wine cooler which I sipped for the rest of night. That wasn't too much, was it?

Master Clinician Note: The counselor senses that Isabel is getting a little anxious about this line of questioning and tries to be reassuring and non-judgmental.

COUNSELOR: Two drinks in one night don't sound like a lot to me. I'm only asking because I want to help you do the best for the baby between now and the time you deliver. So let's see: It seems like you are saying that you mostly drink on special occasions. Is that right?

ISABEL: Yes, those are the times I usually drink, and sometimes when Marco has friends over to watch a game I might have a beer or two.

COUNSELOR: Okay. Can you remember any other occasions when you might have been drinking during your pregnancy?

ISABEL: I drank a little on my birthday in July.

COUNSELOR: Did you go out for your birthday?

ISABEL: No. Marco surprised me when I got home. He made me dinner with flowers and wine and everything.

COUNSELOR: He sounds very thoughtful.

ISABEL: *[Smiling, shrugs a little.]* He can be.

COUNSELOR: So, do you remember how much wine you had that night?

ISABEL: I had maybe two or three glasses. I have read that drinking a little wine would not hurt the baby. I try to be aware not to do anything that would hurt my baby. I drank a little with my first child and he is healthy.

COUNSELOR: I know that, Isabel. No mother would do anything on purpose to hurt her baby. I know how hard you're working to take care of yourself during the pregnancy, and that's really important. Did Marco drink with you on your birthday?

ISABEL: Marco drinks all the time. He drinks beer every day. I'm sure that I'm okay, because you know I'm not like Marco. I don't come home and a have a six pack.

COUNSELOR: Okay. So, you drank these two times before you got pregnant. And right about here is when you would have found out you were pregnant. *[The counselor points to circled first trimester on calendar.]* Are there any other days in these months that you can think of, or any events?

ISABEL: *[Pauses, squirms a little in her chair.]* Well, there was one time Marco and I had an argument about the amount of time he spends with his friends. He goes out on Friday nights and drinks with his friends, doesn't come home sometimes until the next morning. He went out and I had some of my girlfriends over and I wound up getting drunk. I was so bad I was throwing up. I was embarrassed. I had to go to the bedroom and they had a bucket and they were saying "Isabel, are you okay?" But that's the only time I can think of.

COUNSELOR: And what were you drinking then?

ISABEL: We were drinking rum and Coke.

COUNSELOR: Okay, do you know how many drinks you had?

ISABEL: We were drinking and playing cards. I must have had three or four, at least.

COUNSELOR: How many drinks does it take to make you feel high?

ISABEL: It depends. A couple glasses of wine, or one rum and Coke, if it is strong.

Master Clinician Note: The counselor is gradually asking more detailed questions about Isabel's alcohol use. Although Isabel claims not to be a drinker, a pattern of usage is emerging through the use of the calendar. Isabel is bringing up Marco often, so the counselor takes this cue and probes further about her husband.

COUNSELOR: It sounds like whenever you drink it has something to do with Marco. Are there times that you drink by yourself?

ISABEL: No.

COUNSELOR: Okay, so tell me about drinking with Marco.

ISABEL: *[Sighs.]* It's just mostly because we're with friends and I like to do what everyone else is doing. I want to be social. I don't drink every day with him. He'll come home with a six pack and drink beer while he is watching TV or sports. He loves baseball and basketball.

COUNSELOR: So he drinks when he comes home from work. Does he want you to drink with him?

ISABEL: He'll offer me a beer now and then, ya know, but that's his thing. That's what men do. I have too many other things going on. I really drink just a little. I really don't think that I am doing anything that is going to hurt the baby. I don't want to fight with Marco about his drinking or his friends. I have to come here to deal with my other problems.

COUNSELOR: Is Marco excited about the baby?

ISABEL: *[Relaxing a little at the change in subject.]* Oh yeah. Very. I'm excited, too. We're looking forward to this.

COUNSELOR: How do you think it's going to be with his drinking after the baby is born?

ISABEL: I don't know. I doubt he will change.

COUNSELOR: Are you worried about that?

ISABEL: No, he's a good guy. *[She sniffles and wipes her nose.]* He really is. I know you probably think he's an alcoholic or something. That's not how it is. We're not like that. *[She starts crying.]* I love this baby. So does he. We're trying to take care of it. *[Her crying continues, and she gets an anxious expression on her face.]*

Master Clinician Note: Isabel is becoming anxious, and is shifting the topic away from alcohol. This is a signal, or cue, to the counselor that the client is uncomfortable. The counselor needs to acknowledge what Isabel is feeling and be careful about how much further she probes on this issue during this visit.

COUNSELOR: I know you have a lot on your plate and I think you are handling it quite well. You did quite a bit in today's session, and you did very well. I would like to end this session and talk a little about our next session. Would that be alright with you?

ISABEL: Sure.

COUNSELOR: I heard you say you had read something that drinking small amounts of alcohol was okay for a pregnant woman. Is that correct?

ISABEL: Yes, I read it on poster, I don't remember where.

COUNSELOR: I would like to give you something to read. It's short. It's about what can happen when babies are exposed to alcohol before being born. I would like you to read it so we can discuss it in our next session. Is that okay with you?

ISABEL: Sure. The more I know, the more I can protect the baby, right?

COUNSELOR: Absolutely.

Master Clinician Note: The mental health counselor is in a difficult position. Her use of the calendar helped to reveal a pattern of alcohol use by Isabel and her husband that exceeds what Isabel first admitted and is unsafe for the baby. It also helped to establish some of Isabel's triggers for drinking alcohol, which include her husband and being angry.

At the same time, discussing alcohol use and how it can hurt a baby can be an emotional topic for the mother. She is working hard to take care of her baby, and the topic of alcohol may have gone further than she is comfortable with. At the same time, it has been useful, as Isabel seems to be reaching a point where she has begun to question her use of alcohol during pregnancy.

This is a learning moment for the counselor. She can see the value of exploring alcohol use with her pregnant patients, but she also knows that, in the future, she can pay closer attention to verbal cues that indicate a client's discomfort; in Isabel's case, the changing of the topic and the repeated assertions that she doesn't think she has hurt her baby. The counselor should continue the session long enough to bring closure to the topic of alcohol use, while supporting the positive things that Isabel has done to take care of her baby. The door should be left open to come back to the topic of alcohol in future sessions.

If Isabel continues to show a pattern of alcohol use during the pregnancy, the counselor can help her identify other ways to deal with her anger besides drinking (stress management), and help her identify or find support systems in her life other than her husband if he is not being supportive of her abstinence during pregnancy (e.g., a pregnancy peer support group). If a mental health counselor does not feel comfortable addressing these issues, referral to a qualified substance abuse treatment counselor is advisable.

5. INTERVIEWING A CLIENT FOR THE POSSIBLE PRESENCE OF AN FASD (FASD INTERVENTION)

Overview: This vignette illustrates the clues the health care worker is receiving that suggest an impairment and possible FASD. A client with an FASD, with brain damage, will not receive the information from the worker the same way someone without FASD will receive it. The client may not have a diagnosis and may not immediately present as someone with a disability. There are a number of questions the worker could ask to determine whether they need to operate in a different kind of therapeutic environment with the client. The main goal of this vignette is for the health care worker to consider the *possibility* of an FASD, not to diagnose an FASD, which can only be done by qualified professionals. A woman who has an FASD is at high risk for having a child with an FASD.

Background: Marta is a single woman, 19, who recently had a baby, and is being seen at a Healthy Start center by a health care worker. This is the first time they are meeting. The health care worker's colleague asked her to meet with Marta as she knew that the health care worker was knowledgeable about FASD and was known as the office "FASD champion." The colleague has begun to suspect that Marta may need an evaluation for FASD, as she has repeatedly missed appointments or been late, gotten lost on the way to the center, failed to follow instructions, spoken at inappropriate times, and has repeated foster placement and criminal justice involvement in her case history. The only information in the history about Marta's biological mother is that she is dead. The colleague wants the health care worker to conduct an informal interview to assess the possibility of an FASD.

Learning Objectives:

1. To learn how to identify behavioral and verbal cues in conversation with a client that may indicate that the client has an FASD.
2. To learn how to apply knowledge of FASD and its related behavioral problems, in order to reassess clients with troublesome behaviors or concerns for factors other than knowing noncompliance.

Vignette Start

HEALTH CARE WORKER:	Hi Marta, how are you?
MARTA:	Good.
HEALTH CARE WORKER:	Your regular counselor has asked me to meet with you today for a few minutes to ask you a few questions, if that's okay. *[Marta nods in agreement.]* Okay, so tell me how you got here today.
MARTA:	*[Shrugs.]* I took the #10 bus, then I got off and walked.
HEALTH CARE WORKER:	Where did you get off the bus?
MARTA:	Madison Avenue.
HEALTH CARE WORKER:	Did you know you could have taken the bus to Washington Street instead of Madison Avenue? Then you would have been six blocks closer.
MARTA:	*[Shaking her head.]* I didn't know that.
HEALTH CARE WORKER:	Do you want me to write that down for you?
MARTA:	Okay.
HEALTH CARE WORKER:	*[Writes down the information.]* Here, you can keep this in your purse. *[Hands Marta the piece of paper.]*

Master Clinician Note: Individuals with an FASD sometimes exhibit poor working memory. The health care worker is not assuming that Marta has an FASD at this point. However, if she does, it is unlikely that she will remember the information about the bus route, so the health care worker writes it down.

HEALTH CARE WORKER:	Did you pay for your bus ride with cash or a bus card?
MARTA:	Today I paid with cash, but I don't always have it.
HEALTH CARE WORKER:	When are the times when you don't have money?
MARTA:	Sometimes friends borrow it, or other people.
HEALTH CARE WORKER:	What other people?
MARTA:	Well, like last time, a man on the corner asked me for money, so I gave it to him. Then I didn't have any for the bus.

Master Clinician Note: Marta has exhibited a double "red flag" for an individual with an FASD; poor money management skills, and a lack of understanding of consequence (i.e., giving away the money without understanding that she then wouldn't be able to pay for the bus).

HEALTH CARE WORKER: Marta, I'd like to ask you a little more about some of the questions that you were asked when you first came here.

MARTA: Okay, go ahead.

HEALTH CARE WORKER: You told us that your mother is not alive. How old was she when she died?

MARTA: Twenty-five, I think.

HEALTH CARE WORKER: How old were *you* when she died?

MARTA: Four.

HEALTH CARE WORKER: I'm very sorry to hear that you've lost your mother.

MARTA: *[Very matter-of-factly.]* I didn't lose her. She died.

Master Clinician Note: Marta is exhibiting very literal interpretation of language, which is common among individuals with an FASD.

HEALTH CARE WORKER: You're right, that's what I should have said. That was probably a hard time for you. *[Marta nods.]* Did you know much about her?

MARTA: *[Shakes her head and shrugs.]* Not really.

HEALTH CARE WORKER: Do you know if she ever had any kind of problem with alcohol?

MARTA: Like, being an alcoholic?

HEALTH CARE WORKER: Yes.

MARTA: *[Shrugs.]* I heard she drank, yeah.

HEALTH CARE WORKER: Do you know if she drank alcohol while she was pregnant with you?

MARTA: I don't know. *[Pauses for a moment.]* That's a weird question. Why are you asking that?

HEALTH CARE WORKER: Did the question make you uncomfortable? Sometimes when women drink during pregnancy their kids end up having extra challenges. Do you know what I mean when I say challenges?

MARTA: Sure.

HEALTH CARE WORKER: Can you give me an example?

MARTA: *[Shrugs].* I don't know.

Master Clinician Note: Marta has stated that she understands when really she doesn't. Any young person might do this, but it is especially common for individuals with an FASD. Checking for cognition is important with clients that have or may have an FASD.

HEALTH CARE WORKER: Needing extra help in school is an example of a challenge.

MARTA: Right, okay.

HEALTH CARE WORKER: Is it okay to ask a few more questions?

MARTA: Yeah.

HEALTH CARE WORKER: Thanks. This will only take a couple more minutes, I promise. How about you? Do you drink alcohol at all?

Master Clinician Note: Because this is an interview to see if there is reason to believe that Marta has an FASD, the counselor is probing to see if perhaps Marta's baby was also exposed to alcohol before birth.

MARTA: No, I don't like the taste of it.

HEALTH CARE WORKER: Me neither. So, you didn't have any alcohol while you were pregnant?

MARTA: No, my foster mom and dad told me not to drink or smoke while I was pregnant.

HEALTH CARE WORKER: That was very good advice. Tell me, where did you live when you were growing up?

MARTA: First with my aunt, then lots of places. I was in foster care.

Master Clinician Note: It is not unusual for individuals with an FASD to no longer be in the care of their parents, and to have been placed multiple times in foster care.

HEALTH CARE WORKER: Did you like school when you were growing up?

MARTA: *[Looking down.]* Umm… I guess it was okay.

HEALTH CARE WORKER: What classes did you like?

MARTA: I liked art. And I liked Ms. Norton.

HEALTH CARE WORKER: Who was Ms. Norton?

MARTA: Ms. Norton was in the resource room.

Master Clinician Note: Time spent in the "resource room," while not a clear-cut clue, is certainly a strong indicator that the child was identified in school as having special needs. This is often the case with children who have an FASD. The counselor could further explore by asking a follow-up question like "Did you ever have extra help with your school work?" or "Did you ever have special classes or tutoring in school?"

HEALTH CARE WORKER: How many students were in the class with you?

MARTA: Five, including Eddie.

HEALTH CARE WORKER: Who's Eddie?

MARTA:	*[Laughing a little to herself as she remembers.]* Eddie is the kid that I used to get in trouble with all the time. He was always coming up with ideas.
HEALTH CARE WORKER:	What do you mean when you say Eddie "came up with ideas?" Can you give me an example?
MARTA:	Well, like, one time we were walking home from school, and he saw a bike in someone's yard that he really wanted. So he told me to go get it for him. I did, but the man who lived there caught me and called the cops.
HEALTH CARE WORKER:	Did you realize that taking the bike could get you into trouble?
MARTA:	I had a feeling. I wasn't sure, but I wanted Eddie to keep liking me.

Master Clinician Note: Involvement in "trouble" or crime as an unintentional secondary participant is an FASD "red flag," particularly when the motivation is social (i.e., to make friends).

Master Clinician Note: Marta's case/vignette is oversimplified. In a matter of minutes, she has exhibited a handful of behavioral clues that suggest that she may have a disability. Not all individuals who may have an FASD will be this easy to 'spot.' This conversation is provided simply as a way to learn how such "red flags" might come up in conversation with a client. By identifying these red flags, which are particularly common in individuals with an FASD, the health care worker will be able to manage the case in a way that better suits the needs of the client, and can make a better-informed decision regarding the need for a more complete FASD diagnostic evaluation. Additional probing questions that could be asked include the following:

- How much alcohol did your mom drink when she was pregnant?
- Think about when you were a child. How did you do in school?
- Do you ever have trouble keeping appointments? How do you do with telling time?

Refer to Part 1, Chapter 2 for guidance on referring a client for a formal FASD diagnostic evaluation, and for strategies and treatment modifications that will improve treatment success with an individual who may have an FASD.

6. INTERVIEWING A BIRTH MOTHER ABOUT A SON WHO MAY HAVE AN FASD AND IS HAVING TROUBLE IN SCHOOL (FASD INTERVENTION)

Overview: Counseling professionals in mental health or substance abuse treatment may avoid talking to a female client or family member about their alcohol use during pregnancy, either to avoid communicating any shame or judgment to that individual, or out of a lack of knowledge about FASD. This case illustrates a scenario where such a discussion may prove fruitful, and the sensitivity required when starting the discussion.

Background: The vignette begins with a community mental health professional talking to Dixie Wagner, 35, about the behavior of Dixie's 7-year-old biological son, Jarrod. (Jarrod is not present at this session.) Jarrod is in trouble again for hitting another child, and this is causing distress for the mother that the mental health professional wants to address, which leads into a discussion of FASD.

Learning Objectives:

1. Cite methods to help the caregiver clarify the child's issues and discover why the child is having problems.
2. Specify skills needed to follow the caregiver's lead in asking probing questions.
3. Explore the negative perceptions surrounding prenatal alcohol exposure, and examine how lack of knowledge or fear of shaming may interfere with asking the right questions.

Vignette Start

MENTAL HEALTH PROFESSIONAL:	Dixie, we talked briefly on the phone about Jarrod's school issues. It sounds to me like you are concerned for him. Today I'd like to hear more about your concerns, and then we can work from there. How does that sound?
DIXIE:	Yes, that's fine. You're right, I'm very concerned about him.
MENTAL HEALTH PROFESSIONAL:	Is it okay that we talk about the kinds of behaviors that led to Jarrod hitting a fellow student? Was the student a friend of Jarrod's?
DIXIE:	That is exactly what's so disturbing about this situation; it was someone I thought was a good friend, a kid named Garrett. Jarrod looks up to Garrett and talks about him all the time. I was excited that he wanted to be friends with Garrett. I was very surprised to get a call from the principal.
MENTAL HEALTH PROFESSIONAL:	You're right. Friends are so important for all children this age. Has Jarrod been having problems with his peers?
DIXIE:	*[Sighs].* He's always had a hard time getting along with kids his own age. He starts off happy and friendly. He wants everyone to like him. Sometimes I think his enthusiasm might be too much for some kids. Sometimes he says such crazy things. I don't know if he thinks the kids will laugh at what he says or if he is really being serious. Slowly I can see the kids moving away from him. It breaks my heart. He ends up playing by himself. He really wants everyone to like him. He'll talk to anyone! We always say Jarrod has never met a stranger he didn't like. I worry a little that he'll listen to the wrong person when he gets older. Most of the time he's just so sweet and loveable.
MENTAL HEALTH PROFESSIONAL:	Okay, so what I'm hearing is that Jarrod has been having problems making and keeping friends his own age, although he really wants to have a friend. Is that right? *[Dixie nods.]* How about in the school setting? How do you think he is doing in class and with his school work?
DIXIE:	Well, he's been labeled a "talker" in class, and we've gotten plenty of notes from the teacher because Jarrod likes to chat with his neighbors and that annoys them sometimes, and the teacher. He has a lot of energy, and sometimes loses focus on his work. He can get frustrated, and may have a hissy fit

	at school when he doesn't want to do his work. He likes to do a good job. Sometimes he just won't finish his work. So the teacher will send it home for us to do with him. Every night we sit down and spend a lot of time on homework, but that usually ends up in Jarrod fighting and yelling at us.
MENTAL HEALTH PROFESSIONAL:	So, Jarrod generally has a hard time focusing and sitting still. These hissy fits, as you call them, how many of these will he have in a typical school day? Can you tell me a little more about that? Are you noticing any consistent struggles?
DIXIE:	I guess he's had several since starting school this year. The hissy fits are like toddler temper tantrums. I can't believe he is still having tantrums. We never really know why he has them, especially at school. I know he leaves every day happy to be going to school, but when he gets home he's tired and cranky, and very angry. He doesn't know where his homework is in his backpack. This leads to raised voices, either me or my husband. The teacher always tells us Jarrod was given the homework, so he must be deliberately misplacing it. If we do find the homework assignment, Jarrod will sit and work really hard for awhile, but then he starts to whine and cry that he is tired and doesn't remember what the teacher told him that day. My husband and I review his spelling words with him every day. He sits and really tries hard to remember them. But he never passes the test on Friday. We spend lots of time with him on his homework. It's like we have to re-teach him everything he learned from the day. Many times it ends in a hissy fit. It's not like we don't help him. We've done this with him since he was in first grade.
MENTAL HEALTH PROFESSIONAL:	Jarrod sounds like he is facing some challenges with his school work. Are there other times or activities when he struggles?
DIXIE:	Well, when he gets off the bus in the afternoon, he is out of control. He runs around, bumping into furniture and screaming. Sometimes he will knock down the dog. I am sure he doesn't mean to hurt the dog, though, because he really loves it. The teacher says he has trouble standing in line for lunch, and pushes the other students next to him. She also says he has a hard time on the playground for recess. He prefers to stay inside with her. And about 2pm every day, Jarrod gets very sleepy.
MENTAL HEALTH PROFESSIONAL:	I see. Is he getting enough sleep?
DIXIE:	We start the bedtime routine about 7:30, right after dinner. The kids will take showers, brush their teeth, and then we'll read a book together. We struggle to get Jarrod to brush his teeth. He hates taking a shower, but once the water is in the tub, he loves taking a bath. Everyone gets a chance to pick a book when it's their turn. Jarrod always picks a picture book

	about Kermit the frog. But when it is time to go to bed, Jarrod is wide awake, talking or playing his video games. We've had to put him in his own room so my other children can go to sleep. Jarrod is up before my husband, usually before 5am, because he's never needed much sleep.
MENTAL HEALTH PROFESSIONAL:	So what I am hearing is that you and your husband have set up a nighttime routine for all the children, but Jarrod has a hard time with the routine. It sounds like Jarrod is only getting a few hours of sleep at night. This may be a reason why Jarrod is having problems in school, since he is tired, but I would like to hear more from you. What else is worrying you?
DIXIE:	This isn't school-related, but that boy can't keep his room clean! I run a tight ship, and an unmade bed is not welcome. He can never find anything. I raise my voice, and still no results. My other kids listen to me. I have no idea why Jarrod disobeys me all the time.
MENTAL HEALTH PROFESSIONAL:	Can you describe a typical room-cleaning episode?
DIXIE:	I'll say "Did you clean your room?" and he says "Yes" and then I'll go and check and nothing is put away. There are clothes on the floor. Dirty and clean clothes will be in his dresser drawers. The bed is unmade. He'll leave wet bath towels on the floor. And there he sits playing a video game. Nothing is done and he still says "Yup, it's clean!" He just doesn't listen. Sometimes I punish him. That doesn't work, either.
MENTAL HEALTH PROFESSIONAL:	That can't be easy, and I can see where that could be frustrating for you and your husband. Do you think it's a case of Jarrod not having the organizational skills needed to keep his room clean, or that he doesn't understand what you're asking him to do?
DIXIE:	I think he understands, he's just resisting. I know he can do it, but usually not until I stand over him and make him do it, one thing at a time. It's exhausting.
MENTAL HEALTH PROFESSIONAL:	Well, That sounds like a lot of kids Jarrod's age. But what I'm getting at is when you break down the specific tasks for Jarrod—one thing at a time, like you say—he does what he's told and does it correctly. Is that right?
DIXIE:	Yes, we have found that there isn't a better kid when you work with him one-on-one.
MENTAL HEALTH PROFESSIONAL:	You're providing me with a lot of needed detail. Thank you. Knowing his behaviors out of school really does help me understand how we might be able to help him *in* school. I'd also like to follow up on something you mentioned earlier,

	about Jarrod's friends. How is he with kids his own age, besides Garrett?
DIXIE:	Besides the kindergarten twins who live next door, Jarrod has no one to play with. We tried to get him into soccer, but he ran after the soccer ball no matter what side had it and the kids made fun of him. We tried cub scouts with my husband helping out as den leader, but Jarrod would be very bouncy and talkative, grabbing the other kids' project, sometimes breaking them. The kids would be polite, but eventually started to shun him. Eventually he would go off by himself and play with a toy.
MENTAL HEALTH PROFESSIONAL:	This must be hard for you and your husband.
DIXIE:	We were told last year that Jarrod was immature for his age, but the teacher said boys tend to mature later than girls. The teacher wanted to wait and see if Jarrod matured over the year before we did any official school testing.
MENTAL HEALTH PROFESSIONAL:	So, let's recap what we have talked about. Jarrod tries to be social and verbal, is trusting, and wants to be a good friend. He also has trouble cleaning his room, staying on task, and doing his school work, but when he does sit down for homework, he can be very diligent in getting his work done. Then there may be some sensory issues, like brushing his teeth or taking a shower, and the bus tends to be a problem. Of course, we cannot forget the fight with Garrett. Out of all these things, I don't see a child with an aggressive nature. What I am concerned about, though, is that Jarrod might be facing some difficulties that will lead him to get into another fight.
DIXIE:	This isn't making sense to me.
MENTAL HEALTH PROFESSIONAL:	Well, I don't have a real clear picture yet. However, one of things that could be at work is that Jarrod could have some cognitive issues that are creating differences in the way he processes information. These deficits can occur for a whole range of reasons. Sometimes children are born with them, and as they grow, their brains are different from most kids.
DIXIE:	You mean like ADHD? We've had people suggest ADHD before.
MENTAL HEALTH PROFESSIONAL:	ADHD may be one issue, but other things could be at work, too. Is it okay that we talk about before Jarrod was born? This is something that I've asked some of my clients before, and it may be helpful here, as well. I'd like to ask about Jarrod's birth, and when you were pregnant with him. It will help us understand Jarrod's environmental background. Were there any complications during your pregnancy with Jarrod?

DIXIE:	No, everything was fine. In fact it was a pretty easy pregnancy. I didn't have much morning sickness.
MENTAL HEALTH PROFESSIONAL:	Would you say that you planned your pregnancy with Jarrod?
DIXIE:	No, not really. He's our third, and we weren't really planning on a third.
MENTAL HEALTH PROFESSIONAL:	Now, many pregnancies are unplanned. About half in this country, in fact. Were you pregnant for awhile before you knew?
DIXIE:	Yeah, I found out kind of late. *[Starts to become defensive.]* But I had a good doctor, and good prenatal care.
MENTAL HEALTH PROFESSIONAL:	What did your doctor tell you about the use of alcohol during your pregnancy?
DIXIE:	My husband and I are social drinkers, but we always have been. I don't smoke. I drank during my other pregnancies. My doctor even told me to do it sometimes, because I get really stressed out and it's how I used to relax. I really think you're way off here.
MENTAL HEALTH PROFESSIONAL:	Your doctor told you that the occasional drink was okay? That it would relax you?
DIXIE:	Yes, he did, and why would he say that if it wasn't true? He's a pediatrician, for god's sake. Where is this going? Are you saying I did something wrong to hurt Jarrod?
MENTAL HEALTH PROFESSIONAL:	No I do not think you would do anything to hurt Jarrod. Some doctors still give that advice, even though the evidence now suggests that alcohol can harm a fetus. It won't necessarily harm *every* fetus, but it can hurt some. I recognize that this is hard to talk about. I only want to explore the possibility. We both have the same goal, to help Jarrod. He has exhibited a pattern of behavior that makes an FASD something worth examining, even if it's just to rule it out. Do you know about FASD?
DIXIE:	*[Sits forward in her chair, holding up her hands in a defensive manner.]* So, wait. What you're saying is that I drank alcohol and hurt Jarrod while I was pregnant. Is that it?
MENTAL HEALTH PROFESSIONAL:	Only experts can determine whether a person has an FASD. Changes in the brain due to alcohol can only be identified by certain professionals, but what I do suggest is that we start to look at why Jarrod might be experiencing some of the problems that you and his teacher have identified. I am seeing a pattern of behavior that may suggest an FASD. We all want the best for Jarrod, and knowing what is happening in his head may help all of us meet his needs.

DIXIE: *[Leans back, crossing her arms, more relaxed but still wary.]* What is this stuff, FASD?

MENTAL HEALTH PROFESSIONAL: It stands for Fetal Alcohol Spectrum Disorders. See, alcohol is an environmental factor that can affect a developing fetus. I mentioned alcohol because some women are unaware of the effects that alcohol can have on an unborn baby. Scientists refer to the effects of alcohol on the fetus as FASD.

DIXIE: I've never heard of it. Are you saying you think Jarrod has that? *[Sits forward in her chair; tears well up in her eyes.]* What you're saying is that I drank alcohol and changed Jarrod's brain while I was pregnant. Is that it? This is my fault?

MENTAL HEALTH PROFESSIONAL: I'm not leaping to that conclusion. If Jarrod does have an FASD, there is no blame here. I just think it's worthwhile to discuss the possibility, because it may help your son, which is what we both want.

DIXIE: *[Sits back in her chair and slumps a little.]* Yeah, I wanna help him. I want nothing more. My husband and I have done everything we can. *[She sniffles some more and shakes her head, considering; the counselor offers a box of tissues.]* This has been so hard. It's been going on so long. We've seen so many doctors, and heard so many diagnoses, and no one's ever right. Nothing works. But no one's said anything like this before. And when you sit there and tell me that this might all be because I had some drinks while I was pregnant… *[She sniffles some more.]*

Master Clinician Note: It's important at this point for the mental health professional to respond to the fact that the client is feeling blamed and becoming agitated.

MENTAL HEALTH PROFESSIONAL: Then I have to apologize to you. If that's what you're feeling, then I'm to blame, not you. I haven't done my job properly. It's incredibly important to me that you understand that my only goal is to work with you to identify a potential root cause for the problems that Jarrod having, because it's clear that his situation is causing *you* distress. That's all I want to do. There are many cases of FASD. Jarrod would not be the first or the only one. No mother on earth does anything to intentionally hurt her baby. I know you certainly didn't. I have a child of my own. I know the feeling of being a mother, and it's very, very clear to me how much you love your son.

DIXIE: I just… I don't even know what to say. I feel like you're pointing a finger at me. *[She is angry, beginning to cry.]* You're in *mental* health. No offense, but what do you know about *medicine*? Or about my son? About how much I love him? Or about what we've been through? I can't even understand that you're sitting there saying I did this to him.

	I mean, I hear your "no blame" crap, but I'm feelin' real blamed right about now!
MENTAL HEALTH PROFESSIONAL:	Well, like I said, I do apologize if that is how you feel. Maybe we just need to rule out FASD. If it happened, you were going on the advice of your doctor. Would it be alright if we focused on what you want to do next for Jarrod?
DIXIE:	*[Waving her hand to stop the counselor.]* What's it called again?
MENTAL HEALTH PROFESSIONAL:	Fetal Alcohol Spectrum Disorders. FASD. I can give you a pamphlet that talks about the basics of it.

Master Clinician Note: It is advisable to provide FASD information that does not include pictures, particularly of children with prominent facial dysmorphology (e.g., thin upper lip, smooth philtrum). These facial characteristics are present in only a small percentage of children who have an FASD, and if the client's child does not resemble the children in the pictures, this may enable the client's desire to believe that their child can't possibly have an FASD.

DIXIE:	*[Taking the pamphlet.]* So I should read this?
MENTAL HEALTH PROFESSIONAL:	Yes, it would be good if you and your husband both read it and discussed whether you think it describes Jarrod's situation.
DIXIE:	I still say you're wrong. But, what if it does? What happens then?
MENTAL HEALTH PROFESSIONAL:	To start, I think you could begin the process for the school to start testing Jarrod for a learning disability. There are several tests that could help them understand the best way to teach Jarrod so that he doesn't get so frustrated. There are a few pieces of the testing that you will have to complete, like his developmental history, when he walked and talked, things like that. I think you should also look at doing another test for ADHD. In the meantime, we can set up another appointment to talk about FASD, possibly with your husband, as well. And if the two of you are okay with it, I can help you access a more complete evaluation.
DIXIE:	Where does that happen?
MENTAL HEALTH PROFESSIONAL:	It may be best to complete the assessment with a developmental pediatrician at the local hospital. I am sure that doctor will want to see the test results from school. If you like, there is a support group for families called the Circle of Hope. I could give you the phone number or e-mail address for them if you need someone else to talk to who has been through this. How would that be?

Master Clinician Note: Although the mental health professional makes repeated attempts to assure Dixie that she does not need to feel blame about the possibility that Jarrod has an FASD, Dixie has still become upset. This is a very natural response, and counselors should be prepared for birth mothers to feel as though they are being 'blamed' for their child's condition when FASD is discussed. However, many pregnancies are unplanned, some doctors do still recommend a glass of wine as a way for a pregnant woman to relax, and many women do not realize until well into their first trimester that they are pregnant. The mental health professional utilizes these realities as a way to reassure Dixie and disconnect her from a sense of guilt and consistently reiterates their shared goal, to find the best way to help Jarrod. She also effectively coordinates care by putting Dixie in touch with additional testing and offering a support group number.

7. REVIEWING AN FASD DIAGNOSTIC REPORT WITH THE FAMILY (FASD INTERVENTION)

Overview: The purpose of this vignette is to provide counselors with guidance on how to review a diagnostic report (or Medical Summary Report) with family members of a child who has been just diagnosed with FAS.

Background: The client, Jenine, is the caregiver of her grandson, Brice. Jenine is meeting with a counselor from the Indian Health Service to review Brice's Medical Summary Report for the first time. In a prior session, Jenine confided that she felt overwhelmed. Knowing how detailed a Medical Summary Report can be, the counselor suggested that Jenine bring trusted family members and elders to this session. Together they arranged for Jenine's sister, aunt, and an elder to attend.

Learning Objectives:

1. To recognize that clients will need support after an FASD-related diagnosis.
2. To identify how to help the client prioritize the child's and the caregiver's needs.
3. To recognize that the client will need to be educated to understand that the child's behavior problems are due to damage to brain caused by prenatal alcohol exposure.

Vignette Start

COUNSELOR: Welcome, everyone. It is so good for Brice that you could be here. I am very happy to try to answer all of your questions today. We'll go through the basics, so that we can work on what is best for Brice. Does that sound good?

JENINE: Yes.

AUNT: Yes.

ELDER: Yes.

Master Clinician Note: The counselor is listening to everyone in order to validate the feelings and concerns of all individuals attending the session.

COUNSELOR: As I mentioned when you arrived, I am so glad that each of you are here today to support Jenine through this diagnostic process. Together, we can come up with a plan and move forward from there. The plan will build on Brice's strengths, as well as the diagnosis. We'll get started today, but it will take more meetings and community support to understand this diagnosis. A lot of detailed information can be overwhelming, but again, together, we will work through this process.

JENINE: Okay.

COUNSELOR: Before we review the report, let's talk about FAS. What kinds of things have you learned about FAS?

JENINE: I have been reading a lot on the internet.

Master Clinician Note: It is advisable for the counselor to caution the client and all attending the session that the quality and reliability of online information about all forms of FASD varies. She should provide the client with a reading list of up-to-date sources, but advise them to put it down when they need a break to avoid feeling overwhelmed.

COUNSELOR: Okay, I like the internet as a source of information because there can be some helpful sites. At the same time, not all internet information is up-to-date. Here is a list of three Web sites that I recommend. They are updated all the time. They're really the best place to start. The first site publishes some basic facts and I'd like to review that with you all for a few minutes.

Master Clinician Note: The counselor can now review the report with Jenine and her support persons. The counselor can use the review to assess the knowledge level of the client and her sister and elder, in order to determine how much education and support will be needed throughout the process. It is also advisable to inquire about other family members (grandparents, brothers, sisters, aunts and uncles, extended family) to assess how they will feel about the child's disability and to gain insight into cultural differences.

A sample Medical Summary Report can be viewed at the Web site of the Washington State FAS Diagnostic & Prevention Network (FAS DPN): **http://depts.washington.edu/fasdpn/pdfs/4-digit-medsum-web-2006.pdf**.

After completing the review, the counselor should focus on Brice's priority problem area, as well as the most significant need(s) of the caregiver.

COUNSELOR: Okay, now that we've worked our way through the report, we need to focus on the number one area where Brice is having problems. Is that in school or at home?

JENINE: Both, but I can handle home. School is getting out of control. I hope that this diagnosis gets him the help he needs.

COUNSELOR: Well, I know that a diagnosis is not always the pathway to services that we expect. But what I did see in the report was a clear description of Brice's speech and language difficulties, so I think that we can get him the speech therapy services that will help in school.

JENINE: That would be wonderful. Brice stutters, and really has a hard time coming up with the right word on the spot.

COUNSELOR: Okay, then let's make the top priority for Brice to get services and therapy for speech. Does that sound like the best place to start?

JENINE: Yes, let's do that.

AUNT: I will help.

ELDER: We will help, too.

COUNSELOR: Now let's discuss a top priority for you, Jenine. I want to check in with your stress level. If you are stressed, then it will be hard to be truly supportive for Brice. And it is my experience that parents and caregivers of children who have special needs do deal with burn-out.

JENINE: Yeah, that sounds like me.

COUNSELOR: Then since that's the case, let's use a couple of sessions to make a plan. If we have any medical questions, I can consult with a pediatrician to try to get those answered for you. Next, we'll get the speech therapy going for Brice.

JENINE: Okay. How am I going to pay for all of this? All of these services?

COUNSELOR: I know some of that is being paid through your insurance company. I'm more or less the case manager for Brice, so anything not covered, we'll work together to address how those things will get paid for.

JENINE: Okay. Now, what's going to happen in school now, with this diagnosis?

Master Clinician Note: Even though answers to these questions cannot all be provided immediately, the counselor assures the client that they will work together to establish plans to address them.

COUNSELOR: I think that it will be a process, and that will be the focus of our time next week. We'll want to think about how you can best approach the school to get Brice's special needs met. We'll also discuss how to talk to your family and friends as well as his teachers about FAS.

JENINE: Okay.

COUNSELOR: One thing we can definitely do today is make a list of Brice's strengths. It's very important that our plan for helping him focuses not just on his diagnosis but also on his positive abilities. Can you all help me with that?

JENINE: Sure. He has a lot of wonderful qualities, he really does.

COUNSELOR: I know he does. We're going to build on those. So, let's recap. Our first priority is to get the process started on Brice's speech therapy. We also need a plan to help you, Jenine, when you're feeling burned out. We want to talk about payment for services. And we want to address what this diagnosis means in terms of special needs at school. Does that sound right?

JENINE: Yes.

AUNT: Yes.

ELDER: Yes, it does.

COUNSELOR: Good. I'm writing all this down, and I'll give everyone a copy. And we'll set up a time for our next meeting. Let's pick a time that works for everyone.

Master Clinician Note: A diagnosis of any form of FASD can be overwhelming for a family. Although this vignette lacks specifics, the overarching theme of importance is that the counselor is positive, is willing to work with the family to make a plan to address any areas of concern, and is available to help them through the process. For families and caregivers of an individual with an FASD, having this navigational assistance can be tremendously helpful and relieve much of the stress that can go along with caring for such an individual. In addition to addressing the areas identified by the family as priorities, it will be important in future sessions for the counselor to:

- Consistently point out the child's positive attributes;
- Recommend a specific support group for the family, if available;
- Emphasize the need for respite care; and
- Ask the client about ways to involve the child in an area of interest, like music or sports or art. This can provide a 'break' for both the child and the caregiver.

8. MAKING MODIFICATIONS TO TREATMENT FOR AN INDIVIDUAL WITH AN FASD (FASD INTERVENTION)

Overview: The purpose of this vignette is to demonstrate how to modify treatment plans for a client with an FASD.

Background: The client, Yvonne, is an adolescent female with a history of truancy and fighting. She has been mandated to counseling for anger management, and has missed her last two appointments. When the counselor phoned her about the missed appointment, Yvonne's mother suggested that Yvonne may not be taking her medication, and hinted that Yvonne may be depressed.

Learning Objectives:

1. To adjust expectations regarding age-appropriate behavior, since individuals with an FASD may be adult-aged by calendar years, but are much younger developmentally and cognitively.
2. To demonstrate the value of collateral information and how to ask an individual for consent.
3. To demonstrate the importance of seeking involvement from parents and caregivers.
4. To identify how concrete thinking plays a role in comprehension for clients with an FASD.
5. To cite the value of time spent developing rapport and establishing trust.

Vignette Start

COUNSELOR: Hi, Yvonne. We've missed a couple sessions, so I haven't talked to you in awhile. How has everything been going? *[Yvonne does not respond.]* Are you taking your medicine?

YVONNE: Yep.

COUNSELOR: I understand that you are not coming home at night. I'm concerned that on those nights you're not able to take your medicine.

YVONNE: I take my medicine! Can I go?

COUNSELOR: Well, we have more time today, so let's keep talking. You know, I need a break. Do you?

YVONNE: Yes, I want to leave.

COUNSELOR: Well, I don't want you to leave yet, but we can go for a walk. Would you like to walk around the courtyard, or go to the cafeteria?

YVONNE: Outside. I want to walk in the courtyard.

COUNSELOR: Yeah, let's do that. It'll get us out of this stuffy office.

They exit to the courtyard.

Master Clinician Note: Yvonne is clearly confrontational. The counselor is navigating around the resistance by not repeating questions and insisting on answers, and changing the physical environment to one that Yvonne chooses. The counselor then begins a rapport-building process by holding off on treatment talk in favor of getting to know Yvonne personally.

COUNSELOR: So, tell me a little bit about things that you like to do. We've only seen each other one time, and that was a few weeks ago. I'd like to know more about the kinds of hobbies and things you like to do.

YVONNE: I love being outside. I love being with animals. My pets are the best.

COUNSELOR: Mine, too. I have three dogs, all Dalmatians. What kinds of pets do you have?

YVONNE: We have a dog named Scooter, he's a chocolate lab, and we have a cat, Cory. I don't know what kind of cat he is. My brother also has a little lizard, but I think it's pretty gross.

This continues for several minutes. At an appropriate time, the counselor begins to shift the conversation back to treatment issues.

COUNSELOR: Let's talk a little about your treatment plan, what is working and not working for you.

YVONNE: Okay.

COUNSELOR: Sometimes clients do not like to take medication, or they don't remember to take their pills. Do you ever forget to take your medication?

YVONNE: Sometimes.

COUNSELOR: Okay. Well, that's not surprising. Taking medication is hard to remember for a lot of people. Sometimes there are bad side effects, or sometimes it's just a bother.

YVONNE: Yeah, it's annoying.

COUNSELOR: What annoys you about your medication?

YVONNE: I don't know.

Master Clinician Note: The counselor should not leave it at "I don't know," but probe further. With a client who has an FASD, the probes should be very specific.

COUNSELOR: Does the medication make you feel bad?

YVONNE: No, not really.

COUNSELOR: Is it hard to remember to take it?

YVONNE: Yeah. I have a lot of stuff to do, ya know.

COUNSELOR: Yeah, I know what you mean. Ya know, I take a vitamin each day with my lunch. That way, whenever I eat lunch, I know to take the vitamin. They go together. Since I go home for lunch, I keep my vitamins at home on the counter, next to the 'frig. I also put a reminder in my phone so that at noon, my phone says "Take vitamin." I think we could work out a system like that for you, something easy that reminds you to take your medication that won't be annoying.

YVONNE: Okay.

COUNSELOR: Let's start by writing this down.

The counselor works with Yvonne to develop a few simple, concrete steps to help her remember to take her medication. Once back in the office, the steps are written down and then reviewed with Yvonne to make sure she comprehends them.

COUNSELOR: Does that look okay?

YVONNE: Yeah.

COUNSELOR: When did we say you should start using that plan?

YVONNE: Right away.

COUNSELOR: That's right.

Master Clinician Note: The counselor does not merely ask "Does that look okay?" but also asks a follow-up question to make sure Yvonne understands. Since this is a client that has been noncompliant with medication, the counselor also schedules another session at an early date to reinforce the new plan, rather than waiting a week or longer.

COUNSELOR: Okay, let's try this treatment plan for the next few days. I'd like to see you in three days so that we can see how it worked.

YVONNE: Okay.

COUNSELOR: I'll write all this down for you. Also, I'd like to ask that your mom help you with taking the medication. Would it be okay if I talked to your mom after today's session? The three of us could spend a few minutes discussing how she can help you remember to take your medication.

YVONNE: Yeah, that'd be okay.

COUNSELOR: I know she's picking you up today, so let's also ask if she can drop you off for your next appointment.

YVONNE: Okay.

COUNSELOR: *[Reinforcement of rapport-building].* Will you bring me a picture of Scooter and Cory? I'd like to see what they look like.

YVONNE: Sure. I'd like to see your Dalmatians.

COUNSELOR: I'll bring a picture, too. Let's program a reminder into our phones for our next appointment, with a special note to bring pictures.

Master Clinician Note: The counselor has employed a number of steps to build rapport, avoid confrontation, and simplify processes for a client that has an FASD:

- Although clinicians are trained to ask open-ended questions, this counselor made the questions quite specific. For example, when the question "How has everything been going?" got no response (it's a fairly abstract question to someone with an FASD), the counselor avoided confrontation and switched to something specific: "Have you been taking your medication?"
- The counselor never used the word "why." A person with an FASD will most likely struggle with understanding or communicating their motivations.
- The counselor limited choices to avoid overload; for example, instead of "What would you like to do?" the counselor offered a specific choice: "Would you like to walk around the courtyard, or go to the cafeteria?" This simplified the choice for Yvonne, and also changed the environment to one she likes, allowing her to share a little more easily.
- The counselor broke down the medication plan into small chunks, wrote them down, and reviewed the steps one at a time with Yvonne. If Yvonne had not seemed to be grasping the plan, the counselor could have considered reviewing it several more times, or even role-playing to solidify each step.
- The counselor scheduled a quick-turnaround follow-up visit so as not to lose valuable time if the plan isn't working, and is bringing the mother into the process as reinforcement.
- Lastly, the counselor built rapport and found a common ground around something that Yvonne really enjoys, her pets.

9. WORKING WITH AN ADOPTIVE PARENT TO CREATE A SAFETY PLAN FOR AN ADULT MALE WITH AN FASD WHO IS SEEKING LIVING INDEPENDENCE (FASD INTERVENTION)

Overview: The purpose of this vignette is to demonstrate how counselors can help develop a safety plan for clients with an FASD. This vignette focuses on creating a safety plan with a caregiver, as many individuals with FASD have someone in their life who provides advocacy and support. If there is no such person in the life of the client with FASD, an important treatment goal will be to identify persons who can fill that role.

Background: In this vignette, Mike's son, Desmond, is 21 years old, and has been diagnosed with an FASD. Mike adopted Desmond when he was five years old. Since Desmond turned 16, and Mike's wife left him (partly due to the difficulties of parenting Desmond), Mike has been Desmond's sole caregiver. Lately, Mike has become increasingly distressed about his son and life in general, and has sought counseling from a mental health provider.

We are picking up this session after Mike has mentioned that Desmond is excitedly preparing to live on his own, with the move-in date just a month away. Mike is sure his son can't handle all the responsibilities of independent living. He has tried to talk to Desmond about this, his son doesn't seem to listen or agree. Mike is realizing that there is a lot he has not talked about with his son.

The counselor took time to gather a good deal of background information. Mike is here on his own in this visit, but the counselor has met Desmond. Desmond has intellectual abilities in what is called the borderline range (just below average). Like many individuals with an FASD, he acts like someone who is younger. In the first session, when the counselor asked Mike to estimate Desmond's "acts-like" (i.e., functional) age, Mike said that Desmond still acts like someone who might be in 10th grade. As the counselor has gotten to know Desmond, this estimate seems accurate. The counselor has also carefully reviewed Desmond's Medical Summary Report (from age 11) and his latest school testing (age 20, when he graduated from high school). She now better understands his unique learning profile.

Master Clinician Note: Clinical wisdom in the field of FASD, and now some scientifically validated treatments, hold that knowing the unique cognitive/learning and behavioral profile of the affected individual is crucial to understanding the reasons for their actions. This helps to reframe caregiver understanding in light of the individual's brain-based disability.

Mike also told the counselor that Desmond was diagnosed with ADHD at age 8, which helped with an accommodations plan at school and a medication regimen. When Mike tried to transfer responsibility for taking the medication to Desmond 3 years ago, he couldn't remember to take it on his own. When Mike and Desmond's doctor realized Desmond showed no decline in function off the medications, they decided to stop the regimen. Without a clear benefit, and because Desmond could be pressured to give away his stimulants to peers, stopping the medication seemed wise.

Learning Objectives:

1. To show how to identify and validate caregiver concerns, and how to integrate common issues for individuals with FASD in safety planning.
2. To show that safety for a client with an FASD requires a plan that decreases risk, increases protective factors, and focuses on comprehensive life skills planning.
3. To illustrate how to assist caregivers as they proactively develop strategies to ensure their child's safety.
4. To demonstrate that individuals with FASD need a plan that is practical, useful, developmentally appropriate, uses concrete language and visual aids, uses role-play, and takes into account their unique cognitive/learning and behavioral profile.

Vignette Start

[The dialogue starts with the counselor meeting with Mike in an individual counseling session. The counselor requested that Mike come in on his own for this session, but expects to meet with Mike and Desmond together in at least some future visits.]

COUNSELOR: What are your greatest concerns about Desmond living on his own?

MIKE: Well, I've always been there for him, and I'm really concerned that he could get into trouble out there in the real world. He has a lot of good points, and I know Desmond's tough. We got through it when his mom left a few years back. I know he turned 21 and he's *feeling* independent, but I know that he can't *be* totally independent. There's too much stuff I help him with, all the time. But I do need some time of my own. Some days…well…there are those days that

I'm zapped—done. The truth is: I'm at my wit's end. I work my butt off. Besides that, I don't take vacations from being a parent. I've sacrificed. Don't get me wrong, I love him, but there are days…. Well, you know. I'm sorry, my head's somewhere else today.

COUNSELOR: I know how much stress parents of a young person with an FASD can be under, and how much strength it takes to parent a child with a disability, especially alone. Take all the time you need to explain what's on your mind. Sounds like there are many sides to this situation.

Master Clinician Note: Mike's thoughts are somewhat discursive due to stress, and perhaps due to grief about the challenges of his son's upcoming life transition. Creating safety protection for Desmond is an important way to help Mike, but the counselor should remain aware that Mike also has his own needs. Research shows that caregivers have many unmet family needs, often focusing on dealing with the emotional aspects of caregiving. The counselor is allowing Mike to express all sides of the situation. This includes negative feelings, but the counselor is also listening for signs of positive "expressed emotion," deemed to be a protective factor. The counselor is also thinking about how to promote caregiver self-care.

[Mike expresses his concerns for several more minutes. The counselor listens and normalizes, validates and reflects Mike's emotions and thoughts, and also makes clarifying summary comments. Providing Mike with time to express his emotions and thoughts and to have his perspective heard allows the counselor to move ahead with more skills-based techniques. These include problem-solving, identifying social supports, identifying and clarifying treatment goals, and cognitive restructuring.]

COUNSELOR: Okay, thank you. I think I have a sense of your concerns, both for Desmond and for your own situation.

MIKE: Yeah. I mean, this is one tough gig.

COUNSELOR: It is, and feeling "burned out" is natural. At the same time, if Desmond is going to be on his own to some degree, as he moves into his life as a young adult, that means a huge transition for both of you.

MIKE: That's an understatement.

COUNSELOR: The good news is that I can provide you with some strategies to help you cope, in the short-term and the long-term. The key here is that the definition of independence and safety is different for a person with an FASD or other developmental disabilities. I think it's important that we start by identifying one or more advocates or "champions" for Desmond. These can be professionals or family members; people who are willing to help him—and help you—manage various parts of his life. So, who can act as an advocate for Desmond? Who are his supports?

MIKE: I can be an advocate, first and foremost. And so can my aunt. Desmond gets along with her really well and sometimes she has him help at her law office doing filing, that kind of stuff. Also, she is one of the few people he'll talk to when he gets upset or angry, and she's good at calming him down. He also helps out with the middle school football team, so Coach Gray looks out for him, but they don't see each other much in the off-season. But…I think he would still be willing to help Des out. Yeah, I think they can help when I can't. And maybe Des can reconnect with his mom.

COUNSELOR: It sounds like Desmond has a number of advocates and supports, but that he mayneed help with both identifying *when* he needs help and, then, *how* to best communicate to get that help. I am so impressed and pleased that Desmond is involved with your aunt and Coach Gray. That gives Desmond's days and weeks more structure and meaning and more opportunities to connect socially. Everyone likes to feel useful! I bet there are more folks who can act as support persons or advocates. We'll try to figure out all those folks in our next session, and what each support person can do. To help move us along, here is the first page of a worksheet to do at home, to make a list of people you think of, their contact info, and what kinds of things they can help with.

[Shows Mike the first part of the Crisis/Safety Plan Worksheet.]

Think about family friends, any providers that work with Desmond, people who know him in his circles, like other people that help with the football team or friends from the community, kids from his high school youth group, church, anything like that. If possible, it is especially important to find someone in their 20's—more Desmond's age, who has good problem-solving skills, to be a kind of "mentor." Can you bring that back next time?

MIKE: *[Nods, takes the first part of the Crisis/Safety Plan Worksheet.]* I'll try to get it done. I don't know about that mentor idea; can't think of anyone right away. But it does help to write things down. If I don't have time for the worksheet… well, you know.

COUNSELOR: Sounds good. This may be a chance to ask your aunt and Coach Gray for ideas, too, as there may be someone that Desmond already knows that could be a good mentor. In terms of the worksheet, I will leave that to you.

Master Clinician Note: Clinical wisdom, and now some new interventions for caregivers of adolescents and young adults with FASD, such as the *Partners for Success Program* (information available through the CDC-funded FASD Regional Training Centers), hold that mentors can be very useful in intervention. Mentors can be community college students, aides who work in developmental disabilities services, younger relatives or family friends, or students studying to work in social services. A mentor is someone who can act as a very competent peer or a caregiver closer in age to the affected individual. They can build an ongoing and positive relationship, be available for check-ins to provide input and guidance on solving problems with peer relationships and lifestyle problems, and work toward helping the affected individual become more self-aware. They may also be able to connect the individual to pro-social and competent peers, and help find appropriate, positive recreational activities for leisure time.

COUNSELOR: Okay, let me ask you: Have you worked much with developmental disability services to help Desmond with life skills, how to live as independently?

MIKE: No, hardly at all. Desmond doesn't qualify for those kinds of services because of his FASD, and his ADHD diagnosis doesn't help, either. He doesn't have really low scores on his IQ test. And, you know, even though he struggles sometimes, he really tries to be friendly and sociable, and he talks a good game. Sometimes I think his good points actually keep him from getting all the help he needs.

COUNSELOR: It must be hard that others don't always see that he struggles with a lot of things. At that same time, it's good to know that he has so many strengths. Alright then, I think you and I will need to work together to identify the most

important things to think about as Desmond becomes as independent as he can safely be.

MIKE: I think my biggest concern is that others will take advantage of Des. Especially if he has a place of his own and people want to stay with him. He tends to do things like steal to be someone's friend, or fall in with wrong crowds, then it's always him that gets caught. I'm not going to be there to prevent that if he's on his own. I mean, Des is willing to accept help, and that's good, but he may not always realize he needs to ask, especially when he gets worked up.

COUNSELOR: I hear you. That sounds like a really big worry for you, so let's talk about some way to provide safety and structure for Des as he moves into having this new freedom. This will be a safety plan, basically. We'll have to find what works and doesn't work for him, and this will be an ongoing process. We can come up with an initial plan, then when he gets into his own place, we can meet together with Des a few times to modify the plan. We'll kind of be testing it out. Adjusting a plan is always a good idea.

MIKE: I've done a lot on my own, talking with Des about what is an appropriate situation and what's not. Appropriate money use. Appropriate touching. This has been all from me. No doctor or therapist helped me out. I should write a book on it. At least I got through to him about drinking, because he just tells people he's allergic, and so far, so good. But now…well, that's another worry.

Master Clinician Note: For parents of individuals with developmental disabilities, it is very helpful to be proactive. At the same time, "looking forward" is an emotional process. The clinician will have to judge how far ahead the caregiver really wants (and needs) to plan. The clinician also needs to use reflective listening and summary statements to help the caregiver process their own emotional reactions as they do future planning. Beyond this, the clinician can help caregivers plan ahead in a practical way. Because Desmond is a young adult (though functionally an adolescent), and is starting to build an independent life, the clinician can coach Mike on how to help Desmond self-advocate and self-monitor.

One important direction is to coach Mike in creating concrete, behavioral "benchmarks" for his son, so Desmond can show daily or weekly progress and also show his father that he is ready for this life transition. This could include practicing things such as buying groceries as if he were already living on his own, and/or troubleshooting, such as thinking out loud about what to do in real-life situations—e.g., if he gets sick, the toilet starts overflowing, etc. If Desmond resists doing this (which would not be unlikely given his functional age), the counselor can work with father and son to integrate rewards for Desmond after he shows certain behaviors or masters specified tasks. An age-appropriate reward for someone functioning at an adolescent level could be more 'space,' i.e., increased time between check-ins from his father after Desmond demonstrates mastery.

Mike has educated his son carefully about drinking, which is good, but he should think about other areas he needs to talk about with Desmond, as well, including 1) safe sex; 2) communicating clearly with partners about consensual activity; 3) use of cigarettes; 4) use of illicit substances, such as marijuana and other drugs; 5) the consequences of criminal activity; and 6) ideas on what to safely do when Desmond has times of feeling irritable and negative (calming strategies).

COUNSELOR: I'm glad you already laid the groundwork! For now, let's write down some of the ideas you already figured out. We'll make cards. Two kinds, actually. First,

when Des comes in we can make an identity card that says "I have an FASD" for Desmond to give to caregivers, police, co-workers, etc. Then we can make Safety Cards that he can use as reminders in his new routine. The Safety Cards can be one thing to talk to Desmond about when he comes with you to see me. We will also plan to talk about specific behavior benchmarks or things you want to see him doing before he moves out. We can talk to Des about how having him do this will let you be more comfortable giving him space and independence. *[The counselor and Mike work together to identify areas of safety concern for Desmond.]*

Master Clinician Note: Choice and level of language used on Safety Cards will differ depending on the intellectual level of the individual with an FASD. Areas of safety concern may include:

- Household reminders (buying groceries, paying bills, cleaning the apartment, taking out the trash, maintaining personal cleanliness, etc.)
- Useful phone numbers (advocates, police, hospital, primary providers, etc.)
- Transportation (routes, times, and costs)
- Work and school schedules
- Personal and household safety reminders (turning off appliances, locking doors and windows, etc.)
- High-risk behavior warnings (e.g., unsafe sex, alcohol or drug use, getting really irritable and upset)

There are programs for caregivers raising affected youth that have other useful ideas for ways to plan ahead (e.g., the *Families Moving Forward Program and Partners for Success Program*).

COUNSELOR: What else could help you with keeping Desmond safe?

MIKE: Well, I think, as long as he applies these things we're writing down for him and I check in on him regularly, things may go okay. For awhile, anyway. Then I just need to get organized with my aunt and Coach, so they're helping to keep an eye on him. Like I said, he's pretty good about accepting help and listening to us when we give him advice. That's one of the most important things I taught him—*accepting* help. But he really has trouble *asking* for help, or watching for signals that he's getting into trouble.

Master Clinician Note: Research on FASD and, more generally, on developmental disabilities has uncovered important protective factors. Many of these are well-known, such as positive family and peer relationships, appropriate social services and freedom from substance abuse by the individual, peers, or family members. Other protective factors may be less obvious but are no less important. For the caregiver, these include decreased stress and depression, a sense of parenting efficacy, positive expressed emotion and a viewpoint on the affected individual, and adequate caregiver support and self-care. For the affected individual, these include a willingness to ask for (and value) help from others, positive, time-filling extracurricular activities, adequate and refreshing sleep, connections to pro-social and competent peers, a positive self-perception, a sense of meaningfulness through activities such as a job, talents that others recognize and value, spirituality, and more.

COUNSELOR: Will Des be working?

MIKE: He's going to continue as an assistant with the football team as a volunteer. And he can keep helping my aunt. When he gets done with his training, we think he'll be able to do inventory and stocking at the grocery store.

COUNSELOR: Okay. Let's start figuring out how all this is going to work. So, I think it may make sense for you to manage Des's budget, at first anyway, by doing his shopping and grocery list-making until new routines are established.

MIKE: Yeah, I expected that. I'm gonna be checking in on him every day for as long as I need to, then less often if I'm sure he's doing okay. I made sure the apartment isn't far away, even though we have to pay a bit more. He isn't showing a real interest or understanding of all the little things required to live on your own; budgeting, or don't buy all your groceries at the gas station just because that's where you get gas, stuff like that. He can use my car if he asks permission, and tells me where he's going and when he'll be back. Mostly, he's going to be taking the bus. I can't imagine him knowing how to take care of his own car, even though he's a pretty good driver.

COUNSELOR: Clearly, you've already thought a lot of things through! Okay, so, why don't you bring Des next time? That will give me a chance to see if I think he needs the support of his own mental health counselor. With his ADHD, and times he gets irritated, that might be a good idea down the road. He has lots of supports, but we should think about this angle, too.

MIKE: That sounds like a plan. I appreciate your help, Doc. I feel like the load is a little lighter.

COUNSELOR: I'm glad. Remember—if you bring that worksheet back next time we can move forward more quickly with our plan.

Master Clinician Note: This session shows what it is like to work with the caregiver of someone with FASD. A possible future session could include Desmond's aunt and the coach, to create advocacy or "look-out" tasks they could all divide up to help Desmond stay organized while Desmond first starts living on his own. In sessions that include Desmond, the clinician will need to change pace and style. Specific ideas that would help Desmond, and can be used with most other affected individuals:

- Work with the affected individual to identify his or her goals, including how to generate an effective goal, "mini-steps" to achieve the goal, and needed supports.
- Discuss warning signs that they need help.
- Discuss and practice through role-play how to ask for help.
- Create a written Crisis/Safety Plan.

This vignette would play out differently depending on the culture and ethnicity of the caregiver and youth. Research shows there are different expectations for independence and type of family relationships in different cultures. This interacts with the impact of developmental disabilities. In some cultures, for instance, adult children are not expected to move out of the family home, though they will still increasingly assume more leadership and adult responsibilities within the family. In cultures where the extended family tends to be closer, affected individuals may have more resources and support from relatives, or a greater likelihood of available peer models to serve as caregivers or mentors. Research also shows that some protective factors may differ by culture: Attachment to and identification with the values of one's culture of origin is a protective factor for immigrant youth. Yet this can also be a risk: Data suggest that these youths may also be at higher risk for marginalization and discrimination. Recommending involvement in culturally relevant and pro-social leisure time activities can be a productive way for an individual with an FASD to learn about their own culture.

10. WORKING WITH A BIRTH MOTHER TO DEVELOP STRATEGIES FOR COMMUNICATING WITH A SCHOOL ABOUT AN INDIVIDUALIZED EDUCATION PLAN FOR HER DAUGHTER WHO HAS AN FASD (FASD INTERVENTION)

Overview: This vignette illustrates how a social worker can make useful suggestions for a parent or caregiver's first meeting with educators at the beginning a new school year.

Background: The start of the school year is 2 weeks away. Denise is a birth mother who is meeting with a social worker to get some advice on how to educate the school staff about working with her daughter, Elise, who is 11. Elise has recently been identified as having an FASD, although she has been tested as having a "normal" IQ and is in a mainstream learning setting. This social worker was part of the diagnostic team that assessed Elise for FASD, but this is her first time helping with Elise's school issues. Denise is hoping to develop learning strategies that she can discuss with the school staff in an Individualized Education Plan (IEP) meeting.

Learning Objectives:

1. To describe typical challenges that children with an FASD may face in the classroom.
2. To demonstrate how collaboration and creativity can lead to accommodations that result in improved outcomes for a child with an FASD.

Vignette Start

DENISE:	Now that we're gearing up for a new school year, with a new teacher who is also new to the school, I need some tips on talking to her. I want to avoid last year's fiasco with the parent aide who complained that Elise was disrespectful and "the worst."
SOCIAL WORKER:	This will be 6th grade for Elise this year, correct?
DENISE:	Correct.
SOCIAL WORKER:	And what happened last year?
DENISE:	The parent aide was a nightmare from the get-go. I had heard it all before: "Your kid won't listen" or "Your kid isn't motivated" or "Your kid *never* does her homework." I knew this aide was gonna be a problem, but I couldn't be in the classroom because I was working full-time. Poor Elise got in trouble day after day for the same stuff; homework not completed, late to class, missing class, getting in fights. Honestly, I think the parent aide did not get any insight into FASD from the teacher at all.
SOCIAL WORKER:	That's unfortunate, but not uncommon, as you know. Educators will sometimes relate differently to a birth mother than they do to adoptive or foster parents. We've talked about those issues before, and it is something that may come up again.

Master Clinician Note: Whether intentional or not, the birth mother of a child with an FASD can be perceived negatively by others, including educators, for having "caused" her child's disorder. The social worker is gently preparing Denise for this possibility and reinforcing the positive nature of how she advocates for her child.

DENISE: I know. I've been there.

SOCIAL WORKER: Well, it's important to remember that you're a fantastic mom, dealing with issues that not many people would have the courage to handle. You're open and willing to learn, to educate yourself about what will work best for Elise, and she is successful because of all the love and support you give her.

DENISE: Thank you, I appreciate that. When I set up the meeting, do you think you can attend with me?

Master Clinician Note: If the social worker cannot attend an IEP meeting with the client, they should still encourage them to have a support person with them, if at all possible; someone else who is familiar with the caregiving situation.

SOCIAL WORKER: I won't be able to attend with you, unfortunately, but I absolutely suggest that you bring someone with you to all meetings. I recall that your sister-in-law has helped out a lot. Is she available, or a good friend?

DENISE: My sister-in-law is the best, yeah. She'd be a great support. She knows the questions to ask.

SOCIAL WORKER: Great. We'll come up with the suggestions and strategies, and you and Elise and your sister-in-law can talk and jot down any additional key issues that you think of. Definitely include Elise. It's her education, after all. Will she be part of the meeting with the school?

DENISE: We weren't planning to include her in the actual meeting, no. She wasn't in it last year. We do talk to her about the issues, though.

SOCIAL WORKER: Well, she's at an age now where it might be worthwhile to consider including her. She's in middle school now, and at this age it might be beneficial to her to see how caring people are planning her supports. Plus, it teaches her to self-advocate, and she can offer specific information and suggestions about problems she's having, or environmental issue that are bothering her; lighting, noise, etc.

DENISE: Okay, we'll talk to her about joining us.

SOCIAL WORKER: Great. And you're meeting with her teacher only? Are there any volunteers in the class this year?

DENISE: I'm not sure.

SOCIAL WORKER: You might wanna ask. If there are volunteers, it would be great if they can attend, as well.

DENISE: Okay.

SOCIAL WORKER: And be sure to allow enough time in the meeting to discuss concrete solutions. Accommodations can take a lot of time to work out. It shouldn't be left to the end of the session.

DENISE: I'll try to address them right up front. What suggestions do you have?

SOCIAL WORKER: I have a couple suggestions for the meeting itself, and then some examples of free, simple accommodations that can improve Elise's school experience. These go beyond the stuff on a standard IEP form. You did a plan last year, correct?

DENISE: Yes, we did.

SOCIAL WORKER: And she'll be in the same school?

DENISE: Yes.

SOCIAL WORKER: Okay, good. So there's already a record with the school of an accommodation history.

DENISE: Right. And it really is just frustrating to have to do this every year. I'm always surprised that one teacher can be great and the next is like a blank slate.

SOCIAL WORKER: I find that, as well. Many families have to start over every year with the school, transferring information, as school personnel changes each September. At the same time, the child is growing and changing, too. Elise is growing older, and what worked for her last year might need to be revised this year. Also, the accommodations in last year's plan might not have been implemented, at least not fully. Elise can speak to that if she's in the meeting. So, let's go through a few simple things that I've found have worked for other clients and their children.

Master Clinician Note: Denise is clearly frustrated with the educational process, and this is understandable. At the same time, the social worker is tempering this frustration and laying the groundwork for a more successful IEP meeting by helping Denise remember the reasons why annual meetings are worthwhile even if difficult. For the meeting itself, the counselor makes the following suggestions:

- To spotlight the child's aptitudes and hobbies, bring pictures of the child enjoying these activities and/or examples of things they've done or created (e.g., artwork, crafts).
- Parent should be encouraged to "catch more flies with honey than with vinegar." The parent's frustration with the system as a whole should not be targeted at the individuals on the other side of the table.
- Parent should approach the meeting with a mindset of using statements such as "My child needs…" rather than "I want my child to..." The federal law is for educators to meet the child's needs, not the parent's wishes.

DENISE: I like those ideas, thanks. What accommodations were you thinking of?

Master Clinician Note:

- Example 1: Federal law limits schools in terms of sanctioning children who act out as a result of a disabling condition, such as an FASD. If the child is acting out, a Behavioral Modification Plan should be considered instead.

SOCIAL WORKER: This first example is really important because I see so many kids with FASD who get into trouble when they're revved up. As a parent, you probably see this often with Elise, and you know her triggers, but educators won't. I worked with a middle-school-aged child, a boy, and his caregiver. The boy was acting out, hitting the bus driver. The school threatened to get the police involved, and the boy was kicked off the bus. I suggested that he be given time at end of each day to relax. It turned out that one of his favorite places was the library, because he could listen to music, so he ended up being able to use last period to go there and sit with headphones on, and we arranged with the librarian to keep an eye on him and monitor the time for him. We called it his "chill zone." After that, he was always cool for the bus ride home.

DENISE: I like that. Elise gets antsy very easily, especially with headphones on, but she'll sit still to read and draw. The library might work.

Master Clinician Note:

- Example 2: Watch for cases when bad behavior is a result of modeling other children with behavioral issues.

SOCIAL WORKER: Another student I worked with, a girl, was getting out of control during the day. She sat in the front row of her classroom, but the teachers and classroom volunteers still reported that even on a good day she was fidgety, and on bad ones she was practically climbing the walls. I explained that sitting in the front row typically helps children focus, but a child with an FASD can also get distracted by kids nearby. In the girl's class, the rest of the kids in the front row were working on behavioral issues, including ADHD. In this case, the girl was modeling the behavior of these classmates in an effort to make friends. I suggested we move the girl next to a model student who could maybe be her buddy or mentor, and that worked well.

DENISE: That could prove useful, as well. Elise does tend to model other children's behavior.

Master Clinician Note:

- Example 3: Work with the educational staff to think "outside the box" when it comes to accommodations.

SOCIAL WORKER: Educators are generally working from a menu of options when it comes to accommodations; such-and-such is suggested based on what the child's condition is. Now, this menu is fairly long, as you know, but it's still an Individualized Education Plan. It should still be geared to Elise's specific needs. Don't be afraid to suggest ideas that you've found work for her, even if they aren't "on the form." Think about what you've done with her in other environments, like at church or in other social activities.

DENISE: Okay. Thanks for your suggestions.

SOCIAL WORKER: You're welcome. Please call me after the meeting and let me know how it goes.

DENISE: I will, thank you.

Refer to Part 1, Chapter 2 for additional guidance on educational accommodations for individuals with an FASD who are still in school.

Part 2: Administrator's Guide to Implementing FASD Prevention and Intervention

Introduction

This Treatment Improvement Protocol (TIP) is designed to assist not only substance abuse treatment and mental health counselors in providing FASD-informed services, but also the clinical supervisors and administrators who support the work of these professionals. The need for a TIP that addresses FASD prevention and intervention for these settings is clear:

- Individuals with an FASD experience higher rates of substance abuse and mental health issues than the general population (Streissguth et al., 1996; Streissguth & O'Malley, 2000; Astley, 2010). In addition, individuals with an FASD exhibit higher rates of life problems commonly encountered in substance abuse and mental health treatment populations, including higher risk of suicide (Huggins et al., 2008), exposure to multiple traumas throughout the lifespan (Henry, Sloane, & Black-Pond, 2007; Greenbaum et al., 2009), homelessness (Fryer, McGee, Matt, Riley, & Mattson, 2007), and increased interaction with the criminal justice system (Streissguth et al., 1996).
- According to the 2009 *National Survey on Drug Use and Health* (NSDUH), 17.1 percent of women age 18 or over in the U.S. received mental health treatment or counseling in 2009, compared to only 9.2 of men in the same age group (Center for Behavioral Health Statistics and Quality [CBHSQ], 2010), while the *Treatment Episode Data Set* (TEDS) indicates that 33.0 percent of admissions to substance abuse treatment facilities in 2011 were female, more than half of whom (50.5 percent) indicated alcohol as a primary, secondary, or tertiary substance of abuse (CBHSQ, 2013). In addition, an in-depth study of 80 birth mothers of children with FAS revealed that 97 percent had from 1 to 9 mental disorders, and the subset that successfully achieved abstinence was significantly more likely to have received treatment for their mental disorders than the subset who did not achieve abstinence (Astley et al., 2000b).

Thus, these settings are 1) likely to see a high prevalence of individuals with an FASD (and/or their parents/caregivers), and 2) provide an ideal environment for conducting interventions with women of childbearing age to prevent additional incidences of FASD.

The methods and techniques presented in this TIP are appropriate for clients in all stages of recovery and treatment. However, this TIP is not meant to create a 'one-stop shop' for FASD-informed services. An FASD is not a simple category that can be addressed with a simple, categorical response; the disorders in this spectrum cannot be cured, and clients

with an FASD need specialized treatment from a variety of healthcare professionals to function at their maximum potential. At the same time, when treating a substance abuse or mental health issue with a client, the counselors' role is to:

1. Be able to recognize when a client is exhibiting a co-occurring issue (such as an FASD) that can impede treatment success;
2. Address how the physical, cognitive, and behavioral manifestations of that issue interact with treatment; and
3. Develop a collaborative treatment relationship with the other healthcare and social service professionals who do—or potentially can—provide assistance to the client to maximize that person's potential for success, both in and outside treatment.

Like any other co-occurring issue in treatment—trauma, homelessness, etc.—addressing FASD is a fundamental step toward helping the *whole* person and ensuring that he or she does not encounter treatment barriers.

Note: This Implementation Guide follows two tracks; FASD prevention, and FASD intervention. This is because this TIP promotes 1) the screening of all women of childbearing age (whether pregnant or not) in all behavioral health settings for alcohol consumption, to help prevent future incidences of FASD [FASD prevention], and 2) the development of staff skills in recognizing individuals who have or may have an FASD, to be able to more effectively tailor treatment to their needs [FASD intervention]. In Part 1 of this TIP, these topics are treated separately. In the Implementation Guide, they are discussed together, since they each represent organizational change and the core processes involved in making such changes within a program overlap significantly.

1 The Administrative Response to FASD in Behavioral Health Settings

IN THIS CHAPTER

Why SAMHSA Created an Implementation Guide as Part of This TIP

Part 1 of *Addressing Fetal Alcohol Spectrum Disorders (FASD)* provides the tools your clinicians need to begin addressing FASD prevention and intervention with clients. However, an extensive literature review suggests that without specific attention to implementation issues, these tools are likely to go unused or to be used ineffectively (Fixsen, Naoom, Blase, Friedman, & Wallace, 2005). This Implementation Guide will help you ensure that the ideas in Part 1 are put into practice in your program or agency in a way that creates value, both for your agency and your clients. Implementation will require the active support of executive administration and the expertise of clinical supervisors.

Much of the guidance provided in this Implementation Guide will be familiar to readers of TIP 48, *Managing Depressive Symptoms in Substance Abuse Clients During Early Recovery* (Center for Substance Abuse Treatment [CSAT], 2008). TIP 48 provides a useful framework for approaching organizational change, and a significant portion of that framework is reiterated here, but with some important modifications and "tweaks" that are essential to providing FASD-informed services. Another useful resource is SAMHSA's Technical Assistance Publication (TAP) 31, *Implementing Change in Substance Abuse Treatment Programs* (CSAT, 2009).

Why Address FASD Prevention and Intervention?

The value of screening women of childbearing age in behavioral health settings is clear-cut. For any woman who is or may

become pregnant, protecting the health of that pregnancy (or potential pregnancy) is a fundamental health issue for the woman herself. Added to this, alcohol consumption questions are built into most forms of health screening, making exploration of this issue a professional commitment. If pregnant women are part of your client base, ignoring this issue means not fully serving the client.

The case for providing services tailored to individuals who have or may have an FASD may not be as simple, but is equally compelling. The historical perception that an FASD represents permanent brain damage, and thus these people cannot be helped in a mental health or substance abuse treatment setting is only half true: Yes, an FASD *does* represent permanent brain damage; no, it *does not* mean that these people cannot be helped, any more than being homeless or involved with the criminal justice system means an individual cannot be helped in these settings.

An FASD is a co-occurring disorder, and needs to be approached from that perspective. Families are seeking this expertise, even if they don't yet know to call it 'FASD,' and clients in need of FASD-informed services will continue to appear in your settings. There is an active movement in the mental health field toward a recovery focus and a strengths-based focus, toward meeting clients "where they are." This movement is growing in the substance abuse treatment field, as well, as are the trauma-informed and family-centered care movements. An individual who has or may have an FASD fits perfectly into any of these paradigms. Individuals with an FASD *do* want to recover, whether in substance abuse or mental health treatment; they *do* have strengths; they *do* experience trauma (at higher rates than the general population); they *do* have families; and, as with any other client, they *are* capable of responding positively when treatment is tailored to their unique needs.

The Effects of FASD on Recovery

At the same time, it cannot be ignored that clients with an FASD are likely to experience challenges to successful treatment above and beyond those experienced by clients who do not have one of these disorders. The client with an FASD may have difficulty in any or all of the following areas:

- Remembering program rules or following multiple instructions.
- Remembering and keeping appointments.
- Making appropriate decisions by themselves about treatment needs and goals.
- Appropriately interpreting social cues from treatment professionals or other clients.
- Attending (and not disrupting) group activities.
- For those accessing substance abuse treatment, staying substance-free after treatment.
- Interpreting or understanding complex meanings of language or information.

The combination of some or all of these factors may lead a counselor to assume that an individual with an FASD is resistant to treatment (and this assumption is often made). It is essential that staff be able to discriminate between a symptom of an FASD and actual treatment resistance. Clients with an FASD may fully intend to be compliant with treatment and want to do well in recovery, but lack the skills and understanding from the provider to help them meet their unique challenges while participating in a recovery program.

The Benefits to Your Program of Addressing FASD Prevention and Intervention

A growing body of evidence is demonstrating that interventions with individuals with an FASD can be effective, that this population can and does succeed in treatment when approaches are properly modified, and that

these modifications can lead to reduced stress on family/caregivers as well as providers (Bertrand, 2009). Moreover, in a study of 1,400 patients with prenatal alcohol exposure, Astley (2010) found that 9.3 percent presented with no central nervous system (CNS) dysfunction, despite alcohol exposure levels as high as the 10 percent that did receive a diagnosis of FAS. The one factor that significantly differentiated the children with no CNS dysfunction (no evidence of learning or behavior problems) from those with full FAS was a stable, nurturing home environment *with intervention services*.

Addressing FASD also has the potential to enhance the treatment experience for both the individual with an FASD and those around him or her, increase retention, lead to improved outcomes, reduce the probability of relapse, increase engagement rates in aftercare services (alternately referred to as recovery support services), and reduce overall societal costs. In addition to the benefits for the client, addressing FASD as part of your program can potentially lead to increased clinical competence of your staff, an increase in appropriate referrals, increased staff retention, higher levels of staff satisfaction, reduced risk of burnout, and reduced turnover.

Addressing co-occurring disorders is also a key priority for the federal government, state governments, insurance companies, credentialing boards, and accrediting organizations. By starting now to address FASD, you will be better positioned to compete in the future treatment marketplace. Ideally, your agency can become part of the larger community of research practitioners who seek the best ways to help clients more quickly experience a higher quality of recovery. By joining with other agencies in your network, you can coordinate treatment practices and perhaps collaboratively obtain research grants. Many effective treatment practices in both the substance abuse and mental health fields, as in the field of approaches to FASD, are not yet validated through research because agencies do not fully realize the value to the greater treatment community of their unique approaches. However, the body of research around FASD is growing rapidly, and addressing FASD now positions your agency at the front end of an emerging skill area.

Most importantly, addressing FASD provides another possible route to success with a client. Individuals with an FASD are a largely hidden population, yet one that is at an increased risk of presenting in your treatment setting. For every client that did not return for additional appointments, or seemed noncompliant or resistant with no clear explanation of why, or just didn't seem to 'get it,' **a knowledge of FASD on the part of your staff can be the one additional clue that solves that puzzle and enables success for both the client and the program**.

Thinking About Organizational Change

If you have decided to implement some or all of the recommendations in *Addressing Fetal Alcohol Spectrum Disorders (FASD), Part 1*, you, your staff, your clients, and the other agencies and organizations with which you interact may require the development of new treatment protocols and policies, as well as new clinical knowledge, attitudes, and skills. These changes can be rewarding and/or frustrating. Any change in services or approaches to clients will call for a significant change in organizational culture, but will be beneficial to client well-being in the long run.

The box "Key Elements of Assessment and Planning" summarizes the key elements of organizational assessment and planning for change, topics that are discussed in greater detail in Chapter 2 of this Guide.

Key Elements of Assessment and Planning

The following five areas are critical to organizational assessment and change planning.

Current status of the organization relative to targeted change goals	Current practices, staff and administrator competencies, policies and procedures, facilities, etc., will need to be evaluated. These are similar to client assessments that determine the nature and scope of a client's issues and challenges as well as their strengths and assets.
Past experiences with change initiatives	Just as a bad experience in a previous treatment program may color a client's perception of a new program, old experiences with organizational change may affect attitudes toward new efforts. A thorough review of organizational history of change is critical to planning new organizational change.
Ongoing assessment	As in treatment, assessment is not a one-time activity, but rather an ongoing process that includes regular feedback and adjustment of your plans for organizational change and your approaches to facilitating change.
Stakeholders of all kinds	Involve as many clients, stakeholders, and community resources as possible (e.g., boards, staff, funders, clients, community representatives, 12-Step groups). These groups function best when they feel involved, and have a key role in determining how to make the recommended changes work best in daily practice (particularly staff). In addition, the plan should speak to what these groups want and what motivates them for the change: If your staff desires professional growth opportunities, change aimed at providing FASD-informed services can be linked to expanding staff capabilities. Similarly, your board's concern with expansion might be tied to the need for increased capacity if the organization is to address FASD among clients.
Clinical supervision	No stakeholder is more important than the clinical supervisor commissioned to implement the clinical mission and vision of the administrators. This individual's challenge is to help clinicians maintain a high level of best practices, to oversee the application of these practices, and to conduct process and program evaluation for quality control. Supervision should be more instructive and less crisis-driven—proactive rather than reactive—by using such strategies and resources as: • Innovative methods including live, in-session supervision, role-playing, taping, and group and peer supervision; • Regularly scheduled, ongoing clinical supervision; • Checklists and fidelity scales; • Quality skills training; and • Counselor mentoring.

An excellent resource for organizational assessment for change is the Program Change Model discussed by Lehman, Greener, & Simpson (2002; **http://forces4quality.org/sites/default/files/Tool2.1Lehman_Assessing_Agency_Readiness_for_change.pdf**), and its accompanying survey, Organizational Readiness for Change (**http://www.ibr.tcu.edu/pubs/datacoll/Forms/orc-s.pdf**). Their model addresses strategies and tools for assessing institutional and personal readiness and outlines the stages of the transfer process.

Ultimately, the application of these elements may suggest that the best decision is to delay attempting a change and focus instead on organizational climate and readiness. Introducing organizational change before the groundwork has been laid—much like introducing change to a client when they are not at the right stage of readiness—can hinder later change opportunities. However, if you decide to move forward with a change plan, the box "Key Principles of Implementation" provides information on implementation.

Key Principles of Implementation

Principles for implementing the change plan are directly analogous to principles of treatment and recovery in that both are achieved in steps, making it a process rather than an outcome. The following principles of managing change are directly adapted from principles of care that are relevant to providing effective FASD-informed services.

There is no single model or approach to providing FASD-informed services, or for implementing a program of organizational change.	A preconception about how change should occur or inflexibility during the change process is likely to be counterproductive to meeting a client's treatment goals or a program's change goals. Constant vigilance and course corrections will be needed, and should be made in consultation with the same stakeholders who developed the original change plan. Periodic focus groups or meetings with staff, clients, and administration provide excellent opportunities for feedback and give all those involved a voice in the process.
A belief in your organization's ability to accomplish the change plan is fundamental.	As with counselors, an administrator's belief that change can happen (and the ability to communicate that belief) is a central component of the change process.
The change program for an organization should be individualized to accommodate the specific needs, goals, culture, and readiness-for-change of that organization.	Like any treatment plan for an individual who has or may have an FASD, it is critical to adapt and 'personalize' the plan to fit specific organizational needs and culture.
It's about maintenance.	After implementing an organizational change plan, maintenance of the changes is essential, particularly in the first year or two. Flexibility around incorporating staff and client recommendations is critical to buy-in of the change. Newly learned practices and procedures are fragile and will tend to drift. In addition, organizational change almost always brings about some degree of personnel change, which requires up-front planning for the selection and integration of new employees. Equally important, unforeseen barriers may arise. Regular supervision and training boosters are the best insurance that behavior change will last over time. Even when the changes are institutionalized, however, a commitment to continuous quality improvement will help ensure your program's ability to respond to ongoing changes in the needs of your client population and community.

The Challenges of Implementation

Any approach to organizational change should assume that resistance may challenge the process. Specific to FASD, some of the usual forms of staff resistance you may encounter are included below, along with suggested responses that may help staff members to see the change process in a more positive light.

It is also useful to remember that resistance can be valuable to a change effort, as it often springs from legitimate needs and/or concerns. By rolling with resistance, you can identify aspects of your change plan that warrant revisiting or revising.

At the same time, failure to implement new clinical practices often has little to do with resistance to change on the part of staff.

> ***Addressing resistance directly will lessen the likelihood that opposition will spread and influence others.***
>
> - ATTC *Change Book,* 2nd Edition, p. 27

Failure to implement can be a result of issues such as inadequate modeling from administration, lack of follow-through, inadequate training, and many others. Even the best

Resistance	Response
I haven't learned this. When will I have time to do the training?	All changes in programming require new learning, and FASD will be no exception. However, new learning means new and expanded skill sets, which can positively impact professional development and advancement. I will work with you to adjust your caseload so that the training is possible.
How can I tell a pregnant mother not to drink? Her OBGYN/doctor says it's okay.	It is true that some doctors still suggest that the occasional drink is okay. However, the SAMHSA FASD Center for Excellence Web site (**www.fasdcenter.samhsa.gov**) contains evidence-based materials that we can use to communicate the "no safe level" message with clients.
The mother is choosing to harm her baby.	Many women are unaware of the risk of alcohol consumption during pregnancy (see previous statement). In addition, half of all U.S. pregnancies are unplanned, so the mother may not realize the potential harm she's doing. Lastly, if the mother has a problem with alcohol, her 'choice' to drink is no more a choice than it is for any other individual in substance abuse treatment.
How do I adjust this cognitive abstract program for someone who does not have the ability to understand abstract concepts?	You don't have to abandon the techniques you generally use. The FASD training will show you how to modify treatment for these individuals within the framework of your usual treatment approaches.
Why am I making exceptions for this client and not for others? This will require ongoing modification of the treatment plan.	It is better to see modifications to the treatment plan as tailoring rather than 'making exceptions,' as tailoring and ongoing modification are a necessary part of meeting clients where they are.

counselors and administrators are highly constrained by the contexts in which they work. Accordingly, implementation success requires administrators to 1) be proactive in making the new practice fit the context, and 2) create an organizational climate that encourages and supports implementation.

These two tasks are intertwining: Fitting new practices to your context requires a thorough review of your agency's current operations. Such self-examination, in turn, helps create an organizational climate of openness to new ideas and experimentation. Before implementation begins, it is important to create positive expectations among staff. Investing the time to educate staff, express support for the specific implementations, and explore potential barriers and concerns with staff can go a long way toward creating an environment of operational transparency and ensuring staff acceptance of change, especially in the early stages.

Often, the executive staff faces more immediate resistance or ambivalence because the initial groundwork was not done. Moreover, administrators have likely considered the change ideas for some time and expect staff to be at a similar level of enthusiasm and commitment to the proposal. Change is easier to make when those involved:

- Understand why the change is needed and the benefits they will realize;
- See how the new ways will integrate into and honor what has been done previously; and
- Are given motivation strategies for providing ideas and offers of assistance in implementation.

Maximizing the Fit

For a clinical innovation to take hold, it must fit with:

(1) Key characteristics of your target population and community (e.g., values, expectations);
(2) The skills, licensures, certifications, and team structures of your staff;
(3) Your program or agency's facilities and resources;
(4) Your policies and practices;
(5) Local, state, and federal regulations;
(6) Available interagency networks (e.g., needed outside resources, memoranda of understanding); and
(7) Your reimbursement procedures.

Certain kinds of mismatches will impede change. For example, no one would expect successful implementation of an innovation when staff lacks the skills to perform it. However, something as seemingly trivial as a lack of appropriate space or needed audiovisual equipment can also stall an innovation. As with many endeavors, the details are critical.

It is likely that adjustments will be needed both in your agency or program's context and in the ways that the recommendations presented in Part 1 are implemented. Part 2, Chapter 2 of this TIP provides procedures, checklists, and other tools for assessing the fit between the recommendations provided in Part 1 and your program or agency's current context, procedures, and so on. Useful though these materials are, your ultimate success in "maximizing the fit" will depend on creativity, problem-solving skills, and determination and patience in applying them.

The Stages of Organizational Change

Change in a program, just like change for a client, occurs in stages. In the early stages of implementing the recommendations in Part 1, organizations will profit from a climate that promotes:

- A willingness to take risks and try unconventional approaches;
- A willingness to tolerate some ambiguity as the fit between new practices and context evolves;

- An ability to recognize false starts and to abandon approaches that are not working;
- Transparency and inclusion when pursuing change; and
- Appreciation and reward for ideas and implementation.

As noted earlier, the later stages of implementation will be facilitated by:

- A commitment to continuous quality improvement;
- The development of structures that support and reinforce the change (e.g., standardized training for new staff, and continuing education and supervision for all staff);
- Expressions of organizational pride in accomplishment; and
- Institutionalization (in which new practices become everyday practices).

The Role of the Administrator in Introducing and Supporting New Clinical Practices

Chapter 2 of this Implementation Guide presents the tasks you will need to accomplish to implement the changes elaborated in Part 1. Important as these tasks are, successful implementation will ultimately depend on the leadership you provide as they are carried out. The box, "Key Elements of Leadership," provides a summary and leads directly into the more detailed discussions of Chapter 2 of this Implementation Guide.

Key Elements of Leadership

Commitment	If you and your administrative colleagues are not fully committed to making your agency's services more FASD-informed, meaningful change is unlikely to occur. In many ways, attempting change without the commitment of organizational leaders can be worse than no attempt to change at all. Staff will eventually "figure it out" if leaders are only giving lip-service to a new idea. This perception will undermine the current attempts at innovation and may lead to a staff that is reluctant to try new ideas.
Vision	Leadership means having a vision of how the organization will change. This vision should include explicit goals and a clear statement of how conflicts with other organizational goals will be resolved. However, a vision is more than a list of goals. It is a picture of how the organization will look when change has been accomplished—a picture you must paint with words. Developing this vision and the means to communicate it throughout an agency requires effort.
Knowledge	Leadership should include skilled and competent clinicians trained in mental health and/or substance abuse treatment who can direct and supervise services for clients with FASD-related issues. These clinicians should know and appreciate the specific roles that can be played by speech-language pathologists, occupational therapists, licensed social workers, psychologists, physicians, and other behavioral health professionals that are part of a comprehensive network of care for individuals who have or may have an FASD. They should also have an appreciation for the role that FASD can play in interfering with treatment.

Inspiration	Inspirational leaders communicate confidence in the organization's ability to change, enthusiasm and optimism about the change process, and an unwillingness to accept failure. This must be communicated to all stakeholders including current and potential clients, funders, board members, staff, community leaders, community 12-Step participants and programs, and sister agencies. Inspiration not only is a process of oral and written communication, but also involves modeling the attitudes and values you want staff and other stakeholders to adopt. Inspiration also involves getting your hands "dirty;" struggling alongside staff in the day-to-day tasks of making new ideas work.
Appraisal	Finally, leadership means an ongoing and honest appraisal of progress. As noted above and discussed further in Chapter 2, implementing the recommendations from Part 1 of this TIP will require ongoing assessments of progress, including regular formative evaluation of process and outcomes. Periodic reports on how the organization is doing can and should be developed from the assessments and evaluations. These reports should be shared with staff, as should plans for corrective action (when needed). The most effective leaders frame both good and bad news in a positive light; e.g., emphasizing the learning value of challenges and setbacks and reminding staff that it is the organization as a whole, rather than any individual, that is responsible for making change happen. This means that "we still have room to improve" is preferable to "you still have room to improve."

2 Building an FASD Prevention- and Intervention-Capable Agency

IN THIS CHAPTER

Introduction

The resources presented in this chapter have been organized into those related to organizational assessment and those related to planning and implementing organizational change. The change process in your agency or program will require creative and thoughtful adaptation and application of these resources to your specific circumstances. They should be viewed as points of departure only. You should revise or otherwise modify the materials as needed for your organization.

You may also wish to consult with colleagues who have managed organizational change in organizations similar to yours. At this point in the development of implementation strategies for human services, many excellent ideas are still to be found outside the published literature. Your colleagues may have insights or ideas that are equal to or more applicable than those presented in this Implementation Guide.

The *Change* Book, produced by the Addiction Technology Transfer Center (ATTC) Network, provides the basis for the organizational change process presented in TIP 48 and in this TIP. The page numbers referenced in this chapter refer to the Second Edition, 2010, which can be downloaded for free from the ATTC Network (**www.attcnetwork.org**) in English or Spanish (**http://www.attcnetwork.org/explore/priorityareas/techtrans/tools/changebook.asp**).

Additionally, you may wish to consult *Implementation Research: A Synthesis of the Literature* (Fixsen et al., 2005; **http://cfs.cbcs.usf.edu/_docs/publications/NIRN_Monograph_Full.pdf**). This monograph provides a valuable summary of the scientific basis for various implementation practices.

Another resource is SAMHSA's TAP 31, *Implementing Change in Substance Abuse Treatment Programs* (CSAT, 2009).

Assessment and Planning Before Implementation

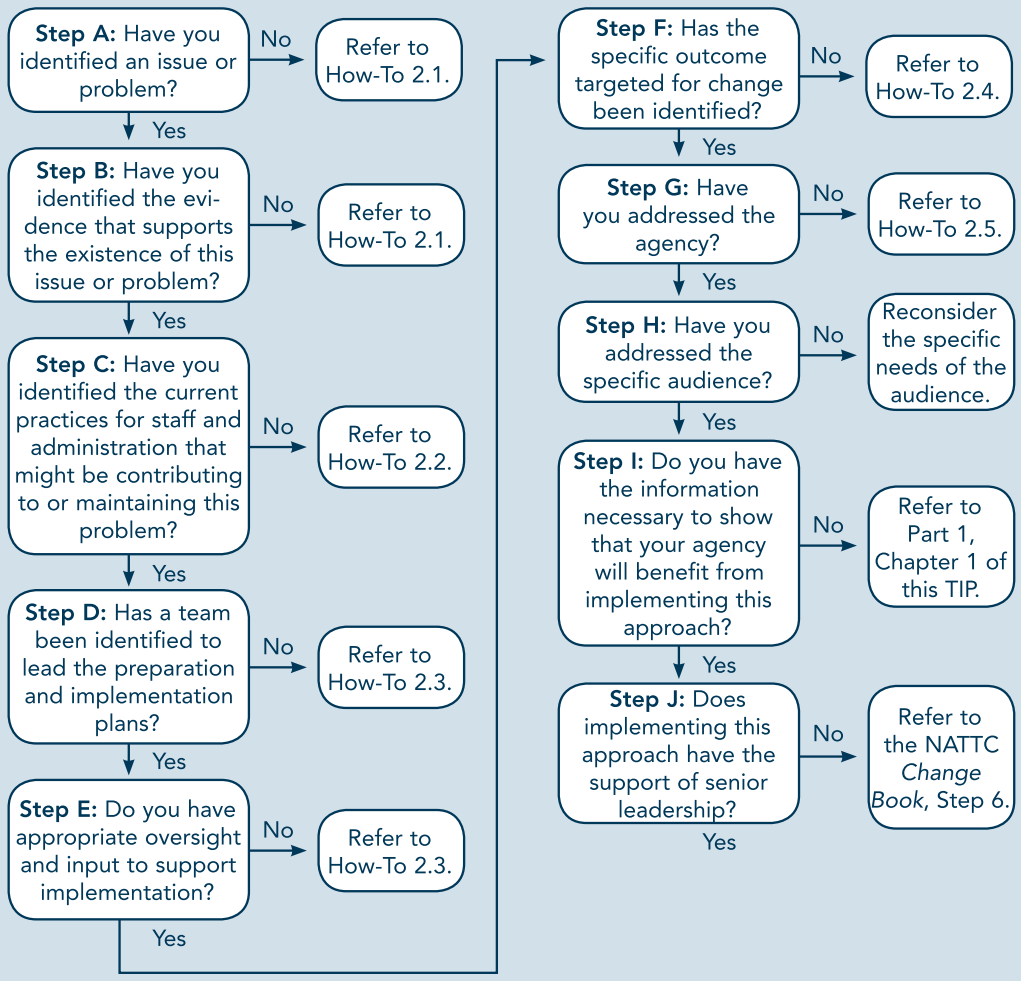
How Do You Decide Whether to Implement a Policy for Addressing FASD?

To determine whether it makes sense for your agency to implement the recommendations made in Part 1 of this TIP, refer to Figure 2.1.

How Do You Identify the Issue or Need?

The How-To components on the following pages provide ways to operationalize the steps presented in Figure 2.1.

Figure 2.1: Decision Tree
How to Decide Whether to Implement a Policy for Addressing FASD



Each of the steps in this figure tie to the How-To's throughout this chapter. (For instance, Steps A and B tie to How-To 2.1, below.)

How-To 2.1: How to Identify the Issue or Need (Figure 2.1, Steps A and B)

Research suggests that the following issues or problems may be relevant to your agency's treatment outcomes. Think about the three levels where change can occur (i.e., program/organizational, practitioner/counselor, and client/patient) when considering the following steps. Also, begin thinking about the part of the agency where you may want to implement changes first (for more information, see also the section *How Do You Decide Where To Start?* later in this chapter).

1. Individuals with an FASD are at higher risk for substance abuse and mental health issues. Determine whether clients who have or may have an FASD are being identified and effectively treated in your agency (see How-To 2.2).
2. People who present with FASD symptoms may take longer and/or require different guidelines and rules to benefit from treatment. Determine whether this is an issue for your agency. Does your program offer the option of longer treatment stays to clients who may have an FASD? Does it offer alternatives to standard policies (e.g., zero tolerance rules) for such clients? If not, how is this need addressed? What practices may need to be changed?
3. Unrecognized symptoms of an FASD result in poorer substance abuse treatment outcomes. Determine whether a goal for your agency is to improve retention rates of clients with an FASD. Determine whether a goal for your agency is to more effectively reduce the number of barriers experienced by these clients.

One aspect of the identification process is to assess the organizational capability of the agency to implement or augment a program for services to clients with an FASD.

How Do You Assess the Capacity of the Agency to Provide FASD Prevention and Intervention?

Individuals with an FASD may see themselves as not fitting in, may be hostile or act out, and may struggle with multiple directions and tasks. Is this addressed in your treatment program? For example, are people failing to make appointments with no clear explanation of why? Speaking at the wrong time during group sessions? Or consistently completing only a portion of the treatment tasks they're given? In terms of prevention, is your program serving pregnant women and/or women of childbearing age? Are these women being asked about their alcohol consumption? Are they being made aware of the risk of FASD? Assess the current capacity of your agency

How-To 2.2: How To Assess Current Capacity to Address FASD (Figure 2.1, Step C)

For each program setting consider the following questions:

1. Has a needs assessment been done to determine the needs of both the clients and the agency?
2. If FASD prevention and intervention have been identified as areas of need, are they adequately addressed in treatment plans?
3. Have key personnel looked into the literature on FASD intervention methods? Are appropriate interventions planned to treat signs of an FASD?
4. Are the FASD prevention and intervention methods already in use (if any) effective with the program's clientele?

5. Are the treatment teams interdisciplinary (e.g., psychiatrist, nurse, licensed master's level clinicians, certified counselors, clinicians, and counselors in training)? If not, your agency can still address FASD through interagency collaboration.
6. Does the supervisory staff have the knowledge, skills, and attitudes necessary to supervise or coach the line staff in addressing FASD?
7. Does the program have referral or consultation relationships with the necessary agencies and professionals (e.g., trained and licensed physicians, physical therapists, occupational therapists, neuropsychologists and speech language pathologists, prenatal care, FASD evaluation/diagnosis teams or agencies)?

Note: For more information on assessing capacity and capabilities, see Sample Policies 1–6 and Checklists 1–4.

or program to deliver FASD prevention and intervention (see How-To 2.2).

How Do You Organize a Team to Address the Problem?

Once you have identified an issue or problem, you need to create a workgroup to address the problem (see How-To 2.3).

How Do You Identify a Specific Outcome to Target for Change?

Once you've organized a workgroup to address the problem, you need to identify a specific outcome to be targeted for change (see How-To 2.4).

How Do You Decide Where to Start?

Once you've identified a specific outcome or outcomes to target for change, you will want the workgroup to assess the agency and the staff (both frontline and supervisory) to be targeted by the implementation. You will have

How-To 2.3: How to Organize a Team to Address the Problem (Figure 2.1, Steps D and E)

1. Identify one person to lead the effort. Many programs that have successfully implemented programming for individuals with an FASD were able to do so because there was one committed, passionate person willing to lead the effort, a 'champion.' This person must have the backing of senior administration and the respect of direct treatment staff.
2. Obtain the commitment of the Chief Executive Officer of the agency to articulate the vision for implementation throughout the agency and with all stakeholders (including clients).
3. Convene an implementation workgroup consisting of key leaders from different stakeholder groups; client leaders, family leaders, team leaders, clinical leaders, and program and administrative leaders. Some stakeholders will serve as ongoing members of the workgroup, while information from others may be solicited through focus groups. If your program has a residential or inpatient component, be sure to include an individual from the night staff (i.e., aide, tech, night nurse). This staff will actually have more conversations with patients than most clinical staff and are in a position to support this program through their observations and understanding.
4. Identify the program oversight committee to which the work group will report. For example, if your agency has a quality improvement committee, the work group may report its findings, recommendations, strategic plans, and modifications to that committee. This is one way to initiate and sustain implementation.

How-To 2.4: How to Identify a Specific Outcome to Target for Change (Figure 2.1, Step F)

1. Begin with the issue or problem identified in Step A of Figure 2.1, and determine a specific variable that can be measured that is directly related to improving the management of FASD. For example, in terms of prevention, the variable may be to "Add FASD awareness as an element of client education with all female clients of childbearing age, whether pregnant or not." In terms of intervention, the variable may be to "Increase staff ability to identify signs of a client who may have an FASD."
    - Identify a way to measure "identify signs of a client who may have an FASD." For example, there is a list of common physical and behavioral manifestations of FASD in Part 1, Chapter 2 of this TIP, and repeated later this chapter, that can be used as a checklist.
    - Identify a way to measure "client education with all female clients of childbearing age, whether pregnant or not." For example, tracking instances of client education on the topic of alcohol-exposed pregnancies, and/or rates of abstention among pregnant clients.
2. Measure a baseline prior to implementing FASD prevention or intervention. For example, determine how many women of childbearing age you see at your agency in a given month. In terms of intervention, review cases of client noncompliance, particularly where no specific cause of the noncompliance is known. Did these clients forget appointments? Not follow directions? Act out? Exhibit family instability and/or have a history of multiple foster care placements? These can become cues for identifying case of possible FASD in the future.
3. Identify which outcome you are most interested in measuring to determine whether implementing FASD prevention or intervention is working. For example:
    - **Intervention**
        - Number of staff trained in FASD intervention methods
        - Rates of identifying potential cases of an FASD
        - Rates of conducting FASD evaluations/assessments
        - Rates of finding/filling FASD assessment slots
        - Diagnoses achieved
        - Follow-up/Aftercare: Family stability over time
        - Multiple foster placements reduced
    - **Prevention**
        - Number of staff trained in FASD prevention
        - Implementation of alcohol screening with all women of childbearing age, whether pregnant or not
        - Treatment planning adaptation based on this screening
        - Achieving abstinence/reduction of at-risk drinking
        - Use of effective contraception by the client

an easier time implementing your plan if you start with a small program where staff members already work well with one another and believe in the new techniques. Staff members on closely knit teams work with one another's strengths and will have an easier time assigning responsibilities when it comes time to implement the practice. Alternatively, you may choose a small, core group of staff members who are ready to try new techniques and are

prepared to be part of an implementation process (i.e., target early adopters across programs). These will be the first staff members trained and coached in using these techniques. Other advantages to starting small include the following:

1. It is easier to track the success of the implementation.
2. It is easier to identify and make any modifications to the techniques that may be necessary to accommodate the agency's clientele.
3. The core group members will talk about the success they are having with the techniques and get other staff interested in learning and using the techniques.

For more information on assessing your agency's readiness for implementation, see How-To 2.5.

How-To 2.5: How to Assess the Agency's Organizational Readiness for Implementation (Figure 2.1, Step G)

1. The committee assesses the agency's organizational readiness by first determining whether implementing practices to improve the management of FASD in the agency's clientele are consistent with the agency's mission statement. (See also the section *Modifying Existing Policies*, this chapter).
2. The committee determines the obstacles to implementation:
   a. Rate of staff turnover in the agency, including average longevity of clinical and support staff.
   b. Inadequate funding for training, technical assistance, and outcome measurement.
   c. Policies and procedures that would have to be changed (see Sample Policies 1–6, this chapter).
   d. Agency facilities and resources.
   e. Federal, state, and local regulations that affect the decision to implement FASD prevention and intervention (see *Addressing Relevant Regulations*, this chapter).
3. The committee determines the opportunities created by implementing FASD prevention or intervention:
   a. Increased funding.
   b. Increased collaboration with other agencies.
   c. Improved community relations and marketing opportunities.
4. The committee determines the organization's stage of change (see also the ATTC's Change Book, p. 29).
5. The committee determines where the resources will come from to provide support for the change initiative (Change Book, p. 29).
6. The committee determines what adoption of this change will mean at all levels of the organization and what the benefits are for administrators, supervisors, and counselors (Change Book, p. 29).
7. The committee determines what is already happening that might lay the foundation for the desired change (Change Book, p. 29). For example, you may already have an FASD 'champion' on your staff.

Addressing Policies and Procedures

Although varying in format and structure as a result of regulatory and organizational diversity, policies and procedures serve as the foundation of organizational practice. Planning and implementing a new program component almost always impacts existing policies and procedures, but those same policies and procedures constitute one of the most common and effective mechanisms for institutionalizing organizational practices. As such, they will need to be reviewed and adapted to be sure they are in conformance with the new program.

Modifying Existing Policies

In addition to adopting policies on addressing FASD, provider agencies might consider modifying other policies and program descriptions to provide continuity of care for (1) women who are or may become pregnant who screen positive for at-risk drinking, and (2) individuals who have or may have an FASD.

For example, each program will develop its own approach to screening and monitoring for FASD based on (a) the characteristics of its clientele; (b) its resources, especially its staff training and background; (c) legal and reimbursement considerations; and (d) other factors unique to your agency (e.g., specific arrangements worked out with referral resources or consultants, participation in clinical trials, or other external influences). Your professional input into developing the necessary policies and procedures is essential, and at a minimum there should be a protocol that stipulates:

- What standard questions a client is asked, when they are asked (by interview and/or self-report mechanisms), and when they should be repeated (especially what observations or events might trigger a fuller evaluation for an FASD)—**These elements of the protocol should use published, reliable tools as discussed in Part 1 and the Literature Review for this TIP** (Appendix C, *Public and Professional Resources on FASD*, contains useful links to sites where tools can be accessed);
- Who can ask these questions and what training is provided or needed regarding the questions and the overall process, procedures, and policies;
- Exactly how scoring or assessment of the clients' responses will be done, including exact guidelines for the follow-up triggered by various responses;
- Where these policies and procedures fit within the agency's policies and procedures and what chain of command and communication exist;
- How long AEP screening and prevention and/or treatment modification for FASD intervention will typically take, which will help you calculate how many interventions one staff member can realistically accomplish per day, anticipate staffing requirements for the project, and project potential income (consult with your administration and billing department—billing for both Medicaid and private insurance may require an intervention of at least 15 minutes' duration);
- How personnel will obtain necessary training, forms, or materials;
- How FASD-informed prevention and/or intervention will be introduced to the client (it might be helpful to have introductory statements worked out and written down in advance, and available to all staff); and
- How FASD prevention and/or intervention will be documented, whether as written or electronic medical record documentation.

This section provides six samples of critical policies and procedures related to addressing FASD prevention and intervention within substance abuse treatment and mental health agencies. In each topic area, a policy statement and set of procedures related to the topic are presented. These sample policies can be used as presented, combined into one or more comprehensive policies, or integrated into the organization's existing policies. Each policy is divided into an example of a policy statement and a set of procedures, as the language will differ depending on whether an agency is revising policies to incorporate FASD intervention or FASD prevention.

Sample Policy 1a

Topic: Clinical staff training and competency [FASD intervention].

Policy Statement: All clinical staff will demonstrate basic competency in identifying signs of an FASD.

Procedures:

1. All clinical and support staff will participate in a 3–5 hour training session covering FASD, the impact of these disorders on treatment, retention, and outcomes, and criteria and procedures for referring individuals to services aimed at formally diagnosing and addressing FASD. (See Appendix C, *Public and Professional Resources on FASD*, for training resources.)
2. The clinical supervisor of new employees will provide site-specific information on the procedures for screening and referring individuals who exhibit signs of a possible FASD.
3. Clinical competency checklists completed at hire and annually thereafter will ensure that all clinical staff members have a basic knowledge of FASD, an understanding of strategies for assessing the significance of FASD, and an awareness of appropriate referral procedures.

Sample Policy 1b

Topic: Clinical staff training and competency [FASD prevention].

Policy Statement: All clinical staff will demonstrate basic competency in screening women of childbearing age (whether pregnant or not) for alcohol consumption.

Procedures:

1. All clinical and support staff will participate in a 3–5 hour training session covering FASD, the impact of alcohol on a fetus, and (if necessary) criteria and procedures for referring women who screen positive for at-risk drinking to appropriate services. (See Appendix C, *Public and Professional Resources on FASD*, for training resources.)
2. The clinical supervisor of new employees will provide site-specific information on the procedures for screening and referring women who screen positive for at-risk drinking.
3. Clinical competency checklists completed at hire and annually thereafter will ensure that all clinical staff members have a basic knowledge of FASD, an understanding of strategies for assessing the dangers of alcohol consumption for women of childbearing age, and an awareness of appropriate referral procedures.

Sample Policy 2a

Topic: Recruitment, training, and supervision of FASD-capable clinical staff [FASD intervention].

Policy Statement: Counselors interested in providing FASD-informed care and who possess the relevant basic counseling skills, knowledge, and attitudes (see Checklist 2, *Characteristics and Competencies of All Clinical Staff*, this chapter) will be recruited, trained, and supervised to deliver these interventions.

Procedures:

1. At least one clinical position in each program or modality of care will be designated to provide FASD-informed care.
2. Individuals exhibiting the attitudes, knowledge, skills, and job performance required to provide FASD-informed care will be identified by their clinical supervisor and designated to provide these services.
3. The counselors identified to provide FASD-informed care will receive an initial training and additional "update" training each year in some or all of the following areas (see Appendix C, *Public and Professional Resources on FASD*, for training resources):
    - Fundamentals of FASD, including the effect of alcohol on the developing fetus and typical cognitive and behavioral impact across the lifespan.
    - Summary of current literature on FASD intervention, and on scientifically validated FASD intervention approaches.
    - Adapting treatment approaches for individuals with an FASD.
    - Talking with individuals with an FASD about their diagnosis.
    - Planning for client safety.
    - Principles of trauma-informed care.
    - Providing a "hands-on hand-off" approach to outside services (i.e., not simply making a referral and assuming that the client takes the appropriate action).
    - Addressing FASD in the context of cultural competency.
    - Building client self-efficacy and self-advocacy
    - Client-centered care.
    - Motivational interviewing.
    - Targeted provider and school consultation.
    - Personal boundaries and professional ethics.
    - Termination, referral, and discharge planning.
    - Appropriate community linkages.
    - Anticipatory guidance and planning for the future.
4. Counselors providing FASD-informed care will receive clinical supervision twice monthly that includes direct observation or review of tapes of individual sessions with clients who have or may have an FASD.
5. Counselors providing FASD-informed care will meet quarterly to provide peer support, supervision, and share resources related to the management of clients who have or may have an FASD.

Sample Policy 2b

Topic: Recruitment, training, and supervision of clinical staff capable of screening women of childbearing age (whether pregnant or not) for alcohol consumption [FASD prevention].

Policy Statement: Counselors interested in providing alcohol screening and referral and who possess the relevant basic counseling skills, knowledge, and attitudes (see Checklist 2, *Characteristics and Competencies of All Clinical Staff*, this chapter) will be recruited, trained, and supervised to deliver these interventions.

Procedures:

1. At least one clinical position in each program or modality of care will be designated to provide alcohol screening to women of childbearing age.
2. Individuals exhibiting the attitudes, knowledge, skills, and job performance required to provide alcohol screening will be identified by their clinical supervisor and designated to provide these services.
3. The counselors identified to provide alcohol screening will receive an initial training and an additional update training each year in some or all of the following areas (see Appendix C, *Public and Professional Resources on FASD*, for training resources):
    - Fundamentals of FASD, including the effect of alcohol on the developing fetus and typical cognitive and behavioral impact across the lifespan.
    - Summary of current literature on FASD intervention, and on scientifically validated FASD intervention approaches.
    - Planning for client safety.
    - Principles of trauma-informed care.
    - Providing a 'hands-on hand-off' approach to outside services (i.e., not simply making a referral and assuming that the client takes the appropriate action).
    - Addressing FASD in the context of cultural competency.
    - Building client self-efficacy and self-advocacy
    - Client-centered care.
    - Motivational interviewing.
    - Targeted provider consultation.
    - Personal boundaries and professional ethics.
    - Termination, referral, and discharge planning.
    - Appropriate community linkages.
    - Anticipatory guidance and planning for the future.
4. Counselors providing alcohol screening will receive clinical supervision twice monthly that includes direct observation or review of tapes of individual sessions with female clients of childbearing age.
5. Counselors providing FASD-informed care will meet quarterly to provide peer support, supervision, and share resources related to providing alcohol screening to female clients of childbearing age.

Sample Policy 3a

Topic: Observation and referral of clients exhibiting signs of an FASD [FASD intervention].

Policy Statement: The possible presence of an FASD will be considered with all noncompliant or resistant or 'problem' clients, and possible indicators will be noted through a process of observation and interviewing. Clients exhibiting signs of a potential FASD will be referred as needed.

Procedures:

1. During intake and throughout the early stages of treatment (i.e., first month), all clients exhibiting persistent (and otherwise unexplained) noncompliance with treatment will be observed, and the individual's case history reviewed, for FASD "indicators" based on a checklist (see the *FASD 4-Digit Code Caregiver Interview Checklist* in Part 1, Chapter 2 of this TIP).
2. Individuals exhibiting signs of an FASD will either be assessed by an identified in-house team with FASD expertise or be referred to an accepted FASD evaluation agency.
3. With or without a formal diagnosis of FASD, a client exhibiting signs of an FASD will be referred to a counselor competent in providing FASD-informed care and capable of modifying treatment to account for the observed behavioral/cognitive deficits (see Sample Policy 2).
4. All screening results, consultation sessions with the clinical supervisor, and referrals (and ongoing communications) to an FASD evaluation agency will be documented in the client's record.
5. The counselor providing FASD-informed care will provide the client with an emergency contact list that includes agency personnel and emergency care providers. The client can refer to this list if he or she has treatment or safety issues outside business hours or when a counselor is not available. (See Appendix F for a *Sample Crisis/Safety Plan* that can be filled out with clients.)

Sample Policy 3b

Topic: Screening and referral of female clients of childbearing age exhibiting signs of an alcohol use/abuse [FASD prevention].

Policy Statement: All women of childbearing age (whether pregnant or not) will be screened for alcohol consumption and referred as needed.

Procedures:

1. During the intake process, all women of childbearing age will be screened for alcohol consumption.
2. Staff will be trained in using specific alcohol screening tools that are validated for use with women, such as the T-ACE or TWEAK (for pregnant women), the AUDIT-C Questionnaire (non-pregnant women), or the CRAFFT Interview or FRAMES (with adolescent and young adult clients).

3. Individuals screening positive for at-risk alcohol consumption will receive an appropriate assessment or be referred for one, to be conducted by a qualified substance abuse treatment professional.
4. Clients who are determined by a qualified substance abuse treatment professional to have an alcohol-related disorder will receive or be referred for substance abuse treatment, also to be delivered by that professional. Collaborative relationships with appropriate providers will be developed.
5. All women of childbearing age will receive FASD-related education (pamphlet, suitable Web site, etc.), whether pregnant or not and whether screening positive for at-risk alcohol consumption or not.
6. All screening results, consultation sessions with the clinical supervisor, and referrals (and ongoing communications) to a qualified substance abuse treatment professional will be documented in the client's record.
7. The counselor providing substance abuse treatment will provide the client with an emergency contact list that includes agency personnel and emergency care providers. The client can refer to this list if she has treatment issues outside business hours or when a counselor is not available. (See Appendix F for a *Sample Crisis/Safety Plan* that can be filled out with clients.)

Sample Policy 4a

Topic: Treatment planning, service recording, discharge planning, and continuity of care [FASD intervention].

Policy Statement: Management of FASD will be integrated with substance abuse/mental health services, be properly documented, and include appropriate discharge and transfer planning.

Procedures:

1. Screening and observation for signs of an FASD and—when indicators are present—strategies for addressing FASD will be included in the client's treatment plan.
2. Treatment plans incorporating FASD management will be jointly developed by the interdisciplinary team and the client within and/or across programs.
3. To minimize client confusion, the client will be provided with information about the roles and responsibilities of those delivering care.
4. Treatment plans will include referral to other community resources and peer support activities that may increase the client's self-efficacy and reduce FASD-related treatment barriers.
5. Interdisciplinary treatment update sessions including all professionals involved with the client's care should occur regularly. (The frequency of treatment plan updates should be consistent with state and organizational standards and will vary by modality of care and regulatory agency.) Ideally these would be held weekly for short-term residential treatment and monthly for long-term residential treatment and outpatient settings.
6. Services delivered by the primary counselor will be recorded in the client's record at each contact and will be available to other members of the treatment team.

7. Major changes in the client's condition or treatment compliance/success will be communicated between the primary counselor and the interdisciplinary team.
8. The checklist of FASD "indicators" (see Sample Policy 3) will be completed at the last session before termination to assist in developing the discharge plan and to be used by the quality assurance department for outcome monitoring.
9. Discharge and transfer planning will include recommendations for the client about self-care, self-advocacy, and other available FASD-informed services that are available to them.

Sample Policy 4b

Topic: Treatment planning, service recording, discharge planning, and continuity of care [FASD prevention].

Policy Statement: Treatment for at-risk alcohol consumption among all women of childbearing age (whether pregnant or not) will be integrated with substance abuse/mental health services, be properly documented, and include appropriate discharge and transfer planning.

Procedures:

1. Screening for alcohol consumption among all women of childbearing age (whether pregnant or not) and strategies for addressing the client's alcohol use will be included in the client's treatment plan.
2. Treatment plans incorporating alcohol use management will be jointly developed by the interdisciplinary team and the client within and/or across programs.
3. To minimize client confusion, the client will be provided with information about the roles and responsibilities of those delivering care.
4. Treatment plans will include referral to other community resources and peer support activities that may increase the client's self-efficacy and reduce alcohol consumption.
5. Interdisciplinary treatment update sessions including all professionals involved with the client's care should occur regularly. (The frequency of treatment plan updates should be consistent with state and organizational standards and will vary by modality of care and regulatory agency.) Ideally these would be held weekly for short-term residential treatment and monthly for long-term residential treatment and outpatient settings.
6. Services delivered by the primary counselor will be recorded in the client's record at each contact and will be available to other members of the treatment team.
7. Major changes in the client's condition or pattern of alcohol use (or simply changes in alcohol use, if this is the primary objective of treatment) will be communicated between the primary counselor and the interdisciplinary team.
8. An appropriate alcohol screening tool agreed upon by the interdisciplinary team will be completed at the last session before termination to assist in developing the discharge plan and to be used by the quality assurance department for outcome monitoring.
9. Discharge and transfer planning will include recommendations for the client about self-care, self-advocacy, and other alcohol use support services that are available to them.

Sample Policy 5a

Topic: Counselor performance appraisal [FASD intervention].

Policy Statement: Counselors capable of providing FASD-informed services will have job descriptions that include a high level of specific performance expectations related to provision of services for these clients.

Procedures:

1. Job descriptions for counselors agreeing/qualified to provide FASD intervention services may include reduced caseload and productivity expectations, particularly during an agreed-upon early stage of implementation.
2. Performance appraisal of counselors providing FASD intervention services will include demonstration of relevant core competencies (e.g., as observed directly and/or through videotaping).
3. Annual training requirements will be outlined in the job descriptions of counselors identified to provide FASD-informed services.
4. Client satisfaction surveys and outcome reports will be discussed in performance evaluations with counselors providing FASD intervention services. Such evaluations may need to occur more regularly than annually when implementing new practice.

Note: The following sample policy is potentially more relevant in mental health treatment settings than in substance abuse treatment settings, as alcohol use management services are a core competency in substance abuse treatment and presumably would not be separated out in a policy statement in this fashion.

Sample Policy 5b

Topic: Counselor performance appraisal [FASD prevention].

Policy Statement: Counselors capable of providing alcohol consumption screening for women of childbearing age (whether pregnant or not) and appropriate services/referral will have job descriptions that include a high level of specific performance expectations related to provision of services for these clients.

Procedures:

1. Job descriptions for counselors agreeing/qualified to provide FASD prevention services may include reduced caseload and productivity expectations, particularly during an agreed-upon early stage of implementation.
2. Performance appraisal of counselors providing FASD prevention services will include demonstration of relevant core competencies (e.g., as observed directly and/or through videotaping).
3. Annual training requirements will be outlined in the job descriptions of counselors identified to provide alcohol use management services.
4. Client satisfaction surveys and outcome reports will be discussed in performance evaluations with counselors providing FASD prevention services. Such evaluations may need to occur more regularly than annually when implementing new practice.

Sample Policy 6a

Topic: Evaluation of service effectiveness and quality assurance [FASD intervention].

Policy Statement: Services for addressing FASD will be reported annually through the agency's quality assurance system along with indicators of effectiveness based on client outcomes.

Procedures:

1. The agency's quality assurance program will include monitoring the implementation of policies related to FASD screening and treatment modifications, FASD evaluation referral procedures, documentation and treatment planning, and supervision of counselors providing FASD-informed services.
2. Data from admission and discharge screening of clients exhibiting FASD "indicators" (see Sample Policy 3) will be aggregated by the quality assurance coordinator for annual reporting to the agency.
3. The following overall agency performance outcomes will be reviewed annually by the management team:
   a. The proportion of clients dropping out of treatment before the third session after implementation of FASD-informed services, or appropriate length of time based on your agency's treatment schedule (it will be important to have information on the dropout rate *after* implementation to assess the impact of these services on treatment engagement and retention).
   b. The number of clients receiving FASD-informed services, as a percentage of overall client population.
   c. The number of clients referred to an FASD evaluation agency, as a percentage of overall client population.
   d. A comparison of (1) the proportion of all clients experiencing a relapse during treatment, and (2) the proportion of all clients receiving FASD-informed care that experience a relapse during treatment.

Note: As with sample policy 5b, the following sample policy is potentially more relevant in mental health treatment settings than in substance abuse treatment settings, as alcohol use management services are already a core competency in substance abuse treatment.

Sample Policy 6b

Topic: Evaluation of service effectiveness and quality assurance [FASD prevention].

Policy Statement: Services for managing alcohol use consumption among women of childbearing age (whether pregnant or not) will be reported annually through the agency's quality assurance system along with indicators of effectiveness based on client outcomes.

Procedures:

1. The agency's quality assurance program will include monitoring the implementation of policies related to alcohol use management among women of childbearing age (whether pregnant or not), substance abuse treatment referral procedures, documentation and treatment planning, and supervision of counselors providing alcohol use management services.

2. Data from admission and discharge screening of clients who are women of childbearing age and have received alcohol use management services (see Sample Policy 3) will be aggregated by the quality assurance coordinator for annual reporting to the agency.
3. The following overall agency performance outcomes will be reviewed annually by the management team:
   a. The proportion of clients who receive screening for at-risk alcohol use who subsequently drop out of treatment, as a comparison with clients who do not receive this screening and subsequently drop out of treatment.
   b. The proportion of these clients evidencing at-risk alcohol consumption at both admission and discharge.
   c. The number of clients who are women of childbearing age who receive screening for at-risk alcohol use, as a percentage of overall client population.
   d. The number of clients who are women of childbearing age who receive services for alcohol use management or a referral to a qualified substance abuse treatment professional, as a percentage of overall client population.
   e. A comparison of (1) the proportion of all clients experiencing a relapse during treatment, and (2) the proportion of all clients who are women of childbearing age and receiving alcohol-use management services that experience a relapse during treatment.

Addressing Relevant Regulations

Another aspect of assessing your agency is to determine whether implementing FASD prevention and/or intervention will conflict with the existing local and governmental regulations and standards that apply to your agency's operation.

For example, both the federal government and individual states have developed their own laws regarding the reporting of cases of known or suspected substance-exposed infants. These laws vary widely in their requirements, but are nonetheless of critical importance to any healthcare setting serving the needs of pregnant women. In addition, providing services to individuals who have or may have an FASD—a recognized disability—carries its own legal and ethical responsibilities.

The following sections discuss relevant regulatory issues related to (1) women who drink during pregnancy, and (2) individuals who have or may have an FASD.

Legal Issues Related to Women Who Drink During Pregnancy

Federal laws related to alcohol use during pregnancy tend focus on prevention and treatment of FASD rather than being punitive. State and local laws vary. Some states, such as Hawaii and Montana, have laws authorizing FASD prevention and treatment programs. Others, such as New Hampshire and Rhode Island, require that information on FASD be available to couples seeking marriage licenses. At least one state, Missouri, requires physicians to counsel pregnant patients about the dangers of alcohol use. It is important for counselors to stay abreast of state laws related to alcohol use during pregnancy and their effect on treatment and recovery.

The Administration for Children & Families, an agency within HHS, provides a searchable guide to state-level statutes regarding the reporting of substance-exposed infants (**http://www.childwelfare.gov/systemwide/laws_policies/state/**).

Custody Issues

Several states (e.g., Florida, South Carolina) do take punitive measures toward alcohol use during pregnancy, such as including prenatal alcohol exposure in their definitions of abuse or neglect. Such measures can be used to remove the child from the parent's custody. Texas allows involuntary termination of parental rights if a woman causes her child to be born addicted to alcohol (other than via a controlled substance legally obtained by the mother by prescription; Section 161.001[1-R]). Generally, a mother who abuses substances may be charged with child neglect or abuse. As a result, her children may be taken from her.

In Virginia, physicians, nurses, teachers, and other professionals are required to report certain injuries to children. For purposes of the law, "reason to suspect that a child is abused or neglected" includes a diagnosis by an attending physician within 7 days of a child's birth that the child has fetal alcohol syndrome attributable to in utero exposure to alcohol (Section 63.2-1509). One state, South Dakota, permits involuntary commitment of a pregnant woman who is drinking.

A number of experts fear that such punitive measures may discourage pregnant women with alcohol problems from seeking treatment. Many states take a more supportive approach:

- Arizona (**http://www.azleg.state.az.us/ars/36/00141.htm**)
- California (**http://law.justia.com/codes/california/2005/hsc/11998-11998.3.html**)
- Washington state (**http://apps.leg.wa.gov/RCW/default.aspx?cite=70.83C.005**)

These three states give pregnant women priority for alcohol treatment slots or otherwise provide access to treatment. Others (e.g., California) provide outreach or case management to pregnant women with substance abuse problems. California also may cover residential treatment for pregnant women under Medi-Cal. In addition, Iowa prohibits discrimination against pregnant women seeking alcohol treatment (**http://www.legis.state.ia.us/IACODE/2001SUPPLEMENT/125/32A.html**).

State and federal governments have established various policies in response to the risks associated with drinking during pregnancy. Among these are various arrangements to increase access to substance abuse treatment by pregnant and postpartum women. Such arrangements include state-run treatment services, funding for private providers, and mandates that such women receive a priority for available treatment. The Alcohol Policy Information System (APIS) addresses statutes and regulations mandating priority access to substance abuse treatment for pregnant and postpartum women who abuse alcohol. In addition, the SAMHSA FASD Center for Excellence Web site provides an FASD legislation report that is updated twice a year.

State statutes that remove custody from birth mothers of children with an FASD are designed to protect the children. However, the threat of losing custody can interfere with the woman's recovery, or cause her to leave prenatal care and/or treatment. The goal is to remain alcohol-free long-term and acquire parenting skills needed to retain child custody and have a healthy, intact family. When screening or referring pregnant women for substance abuse treatment, counselors will need to be familiar with the laws in his or her state and their impact on efforts at family reunification and client recovery.

Child Abuse Prevention and Treatment Act (CAPTA)

One of the most significant pieces of legislation impacting the provision of services to pregnant women is the Child Abuse Prevention and Treatment Act, or CAPTA (P.L. 93-247). Most recently reauthorized on December 20, 2010 (S 3817), CAPTA is designed to protect rather than punish women who give birth to substance-exposed infants. The intent of these reporting laws is that "The newborn and their families will be brought to the attention of the child protective agency in the community, and they will ideally receive needed services within their community" (Burke, 2007).

A new CAPTA state grant eligibility requirement modifies earlier CAPTA language that mandates identifying and making appropriate referrals by healthcare providers to child protective services—and developing service 'plans for safe care' of the child—of newborns affected by prenatal drug exposure. Added as a new category of 'referral' and 'safe care plan' requirement are newborns diagnosed with an FASD. This CAPTA amendment was not meant to cover all situations where a newborn's mother drinks alcohol during her pregnancy, but rather those where a newborn has facial characteristics, growth restriction, or other abnormalities (birth defects) caused by prenatal alcohol use.

This new CAPTA provision (and the earlier requirement regarding drug-exposed newborns) is not intended to have states make prenatal alcohol or drug exposure a category of child abuse or neglect or to make those children subjects of mandatory reporting laws. Congress carefully chose the word "referral" to avoid that. Rather, the goal is to address the safety and well-being of these children. Intervening early through safety plans that promote the health and well-being of these children will be key.

The U.S. Department of Health and Human Services (HHS) provides a comprehensive guide to the CAPTA legislation and its impact on service provision, as well as its implications for community-based family resource and supports grants (**http://www.childwelfare.gov/systemwide/laws_policies/federal/index.cfm?event=federalLegislation.viewLegis&id=142**). CAPTA is also discussed in Part 3 of this TIP, the online literature review.

Territorial and Tribal Laws

At this time, no U.S. Territories have laws related to alcohol use during pregnancy. Tribal laws vary, but the Indian Child Welfare Act (**http://www.nicwa.org/policy/law/icwa/ICWA.pdf**) requires the Indian Health Service (IHS) to make residential treatment available for pregnant women with alcohol problems. In addition, the definition of 'health promotion' in the Act includes FASD prevention. The Act also allows the IHS to make grants to tribes and tribal organizations for various FASD prevention efforts, including alcohol treatment for high-risk women. It also has provisions related to educating Native women about FASD.

Counselors working with Tribal populations will also want to consider the implications of the Tribal Law and Order Act (TLOA) of 2010 and the Indian Health Care Improvement Act (IHCIA), which was made permanent in 2010. Both seek to strengthen access to care and protection of personal rights among Tribal populations, particularly women.

Information about the TLOA can be accessed at **http://www.narf.org/nill/resources/tloa.html**.

Information about the IHCIA can be accessed at **http://www.ihs.gov/ihcia/**.

Confidentiality Issues

Laws such as the Health Insurance Portability and Accountability Act (HIPAA) may affect activities such as reporting of alcohol use during pregnancy. HIPAA has certain requirements regarding privacy and sharing of client information and records. Confidentiality laws vary by state and may affect the addiction professional's ability to share information with various social, health, and legal systems, such as child welfare agencies.

It is essential to be familiar with confidentiality laws in one's state and to consult with an attorney if necessary. Inappropriate reporting of current or previous alcohol use during pregnancy can jeopardize long-term recovery and can harm a counselor's career.

Legal Issues Related to Individuals with an FASD

The most prominent regulatory issue related to individuals who have or may have an FASD is to recognize their rights as individuals with (or potentially having) a recognized disability.

Americans with Disabilities Act Compliance in Treatment Plans

The Americans with Disabilities Act (ADA) of 1990 is a federal law that prohibits discrimination on the basis of disability in employment, state and local government, public accommodations, commercial facilities, transportation, and telecommunications. An individual with a disability is defined by the ADA as a person who has a physical or mental impairment that substantially limits one or more major life activities, a person who has a history or record of such an impairment, or a person who is perceived by others as having such an impairment. Treatment facilities cannot discriminate on the basis of a disability. Many individuals with an FASD will have cognitive disabilities that meet the definitions set forth by the ADA; in any case, such individuals should receive treatment that recognizes their condition as a disability that should not be discriminated against.

Counselors will need to incorporate accommodations for persons with an FASD into any treatment plans. For example, lighting at meetings may need to be dimmed to keep the person with an FASD from becoming overstimulated. Reading materials may need to be adapted to a lower literacy level to accommodate cognitive deficits. More information on accommodating disabilities can be found in Appendix D of TIP 29, *Substance Use Disorder Treatment for People With Physical and Cognitive Disabilities* (CSAT, 1998; **http://www.ncbi.nlm.nih.gov/books/NBK64881/**). Part 1, Chapter 2 of this TIP discusses accommodations specific to individuals who have or may have an FASD.

More information on the ADA can be found at **http://www.ada.gov/**. For technical assistance related to ADA requirements, visit **http://www.ada.gov/taprog.htm** or contact SAMHSA's FASD Center for Excellence toll-free at 1-866-STOPFAS or by visiting **www.fasdcenter.samhsa.gov.**

Addressing Staff Competence

Where Is the Clinical Expertise in Your Agency?

Change in clinical practice is best facilitated by assessing the skills of well-trained and experienced clinicians and targeting them for training and/or enlisting them in helping less skilled counselors facilitate change. Two clinical management structures are described here—interdisciplinary teams and traditional clinical supervisors.

Interdisciplinary teams are one effective way to ensure that the expertise for providing FASD-informed treatment is available in your agency (Clarren & Astley, 1997; Clarren et al., 2000). If you have interdisciplinary teams in your program, the teams assume the responsibility

of tailoring interventions to an individual client's needs in a way that addresses FASD seamlessly. Such teams provide ongoing support, education, and treatment planning assistance for all staff. Teamwork creates an enriched environment for implementing FASD-informed techniques.

If your agency has an interdisciplinary team format for responding to other issues, this may be adapted to FASD. With an interdisciplinary team, you have an advanced level of capability for addressing FASD prevention or intervention in clients with substance use or mental disorders. This assumes that the more experienced and skilled members of the team have the knowledge, skills, and attitudes required to apply FASD-informed interventions and to supervise and coach application of an intervention for other counselors.

Many treatment agencies do not have interdisciplinary teams and instead rely on the expertise of *clinical supervisors* to evaluate and support the work of line staff. Clinical supervisors must have the knowledge, skills, and abilities required to apply an intervention and be able to demonstrate the intervention before they can coach others to perform it. The supervisors must also have the time to supervise and coach the staff. If this describes the supervisors in the setting where you work, you have an intermediate capability to provide FASD-informed care. If the supervisors have not yet reached this level, then you have a beginning capability for implementing FASD-informed care and must develop a plan to build the resources necessary to increase capacity.

The Frontline Staff and Clinical Supervisors

Once you've assessed the agency, you may want to assess the staff who will actually implement the change (see How-To 2.6).

Staff Qualifications and Competencies

As a part of implementing FASD-informed services, a number of process-oriented tasks

How-To 2.6: How to Assess the Frontline Staff and Clinical Supervisors for Change (Figure 2.1, Step H)

The committee determines the specific program and staff members who will be the first to implement change.

1. Are there incentives/organizational supports for change (ATTC Change Book, p. 29)?
2. What are the barriers to change (ATTC Change Book, p. 28)?
3. At what stage of change is the program staff (ATTC Change Book, p. 29)?
4. How will staff practice be affected (ATTC Change Book, p. 29)?
5. What additional support will staff need (ATTC Change Book, p. 29)?
6. Does staff have the prerequisite knowledge, attitudes, and skills?
7. What training and continuing resources are necessary to provide the core intervention com ponents?

See also Sample Policies 1–6 and Checklists 1–4 in this chapter for additional information to be used in assessing staff readiness. See Appendix C, *Public and Professional Resources on FASD*, for links to training resources.

should be completed, including an assessment of initial staff competence, education and training, development of skills and resources, and supervision. These considerations are relevant not only to the counselors' ability to deliver the services but also to clinical supervisors, other clinical staff, and support staff responsible for recording and billing services.

Compared with those providing support services, however, the required level of knowledge and skill is significantly different for those directly involved in clinical care. For this reason, the attitudes, knowledge, and skills required to provide FASD-informed services are separated into four categories:

1. Administrative and support staff
2. All clinical staff
3. Counselors designated to provide FASD-informed services
4. Clinical supervisors overseeing the counselors who provide these services

The four checklists that follow serve two purposes. First, they can be used to assess staff and organizational readiness to implement or sustain FASD-informed services. Second, they can be used to identify gaps in training and supervision to be addressed with individuals or groups.

Addressing Gaps in Staff Capacity to Deliver Services

Not all clinical staff are ready, willing, or able to address co-occurring issues such as FASD. The clinical supervisor is charged with helping staff and administration differentiate the level

Checklist 1: Characteristics and Competencies of Administrative and Support Staff

Attitudes

_____Integrating FASD-informed care is important for promotion of the agency mission.

_____FASD prevention and intervention constitute valid and important experiences for our clients and deserve and require specialized attention.

Knowledge

_____Recognizes the relationship between FASD-informed care and treatment effectiveness.

_____Recognizes how provision of FASD-informed services fits in the mission and goals of the organization.

_____Is familiar with the policies and procedures related to recording and billing services for FASD-informed services.

_____Recognizes the distinction between a person formally diagnosed with FAS/pFAS/ARND and the general signs of an FASD in an individual.

_____Knows the agency's policies and procedures on providing FASD-informed services as they relate to the specific position (e.g., administrative staff in clinical records are familiar with documentation requirements for these services, and the finance staff are knowledgeable about how services are defined for billing purposes).

_____Understands the role of self-help and support groups in recovery and how those groups can support the goals of the program in providing FASD-informed care.

Skills

_____Communicates to the public the role of specialized services related to FASD prevention/intervention.

_____Identifies the 'indicators' of an FASD listed in the screening policy and procedure (see Sample Policy 3).

_____Administers FASD screening and observation properly.

_____Conducts basic client education session on the relationship between substance abuse/mental health issues and FASD.

_____Conducts basic client education sessions with all female clients of childbearing age (whether pregnant or not) on the relationship between alcohol use during pregnancy and the risk of an FASD.

_____Collaborates with other team members on treatment and discharge planning.

_____Conducts a suicide risk screening.

Checklist 2: Characteristics and Competencies of All Clinical Staff

Attitudes

_____Integrating FASD-informed care is important for promotion of the agency mission.

_____FASD prevention and intervention constitute valid and important experiences for our clients and deserve and require specialized attention.

_____Clients have a central role in creating and shaping their treatment goals.

_____Substance abuse/mental health issues and FASD can be both interrelated and independent; resolving one set of concerns may not lead to resolution of the other set of concerns without specialized treatment.

_____There is no one "right" approach to addressing FASD in our clients.

_____Individual sessions can be particularly valuable for clients who have or may have an FASD and can provide an effective adjunct to group treatment.

Knowledge

_____Recognizes the relationship between FASD-informed care and treatment effectiveness.

_____Recognizes how provision of FASD-informed services fits in the mission and goals of the organization.

_____Recognizes the distinction between a person formally diagnosed with FAS/pFAS/ARND and the general signs of an FASD in an individual.

_____Knows the agency's policies and procedures on addressing FASD prevention/intervention.

_____Recognizes the interrelationship between substance abuse/mental health issues and FASD.

Skills

_____Communicates to the public the role of specialized services related to FASD prevention/intervention.

_____Identifies the 'indicators' of an FASD listed in the screening policy and procedure (see Sample Policy 3).

_____Administers FASD screening and observation properly.

_____Conducts basic client education session on the relationship between substance abuse/mental health issues and FASD.

_____Conducts basic client education sessions with all female clients of childbearing age (whether pregnant or not) on the relationship between alcohol use during pregnancy and the risk of an FASD.

_____Collaborates with other team members on treatment and discharge planning.

_____Conducts a suicide risk screening.

Checklist 3: Characteristics and Competencies of All Clinical Staff

Attitudes

_____Integrating FASD-informed care is important for promotion of the agency mission.

_____FASD prevention and intervention constitute valid and important experiences for our clients and deserve and require specialized attention.

_____Clients have a central role in creating and shaping their treatment goals.

_____Substance use/mental health issues and FASD can be both interrelated and independent; resolving one set of concerns may not lead to resolution of the other set of concerns without specialized treatment.

_____There is no one 'right' approach to addressing FASD in our clients.

_____Individual sessions can be particularly valuable for clients who have or may have an FASD and can provide an effective adjunct to group treatment.

_____Resistance to change from clients is surmountable within the influence of the counseling relationship.

_____The client is an integrated whole rather than one or more diagnoses or sets of symptoms.

_____A desire exists to deliver services to clients who have or may have an FASD along with a substance abuse/mental health issue.

_____A desire exists to deliver FASD-informed care to female clients of childbearing age (whether pregnant or not).

Checklist 3: Characteristics and Competencies of All Clinical Staff

Knowledge

_____Recognizes the relationship between FASD-informed care and treatment effectiveness.

_____Recognizes how provision of FASD-informed services fits in the mission and goals of the organization.

_____Recognizes the distinction between a person formally diagnosed with FAS/pFAS/ARND and the general signs of an FASD in an individual.

_____Demonstrates a nuanced understanding of the relationship between substance use/mental health issues and FASD.

_____Recognizes the distinctions among screening, assessment, and diagnosis of an FASD.

_____Knows the common approaches to addressing FASD in substance abuse/mental health treatment settings including motivational interviewing, accommodations, parent/personal navigator, and the importance of coordinated care.

_____Recognizes how FASD presents in ethnic and other cultural groups encountered in the agency.

_____Knows community resources (particularly substance abuse/mental health, primary care, FASD service providers, school contacts when applicable, family/caregiver navigators).

_____Understands how 12-Step and other mutual-help support programs can support someone with an FASD.

_____Is aware of the role of transference and countertransference in the counseling relationship.

_____Recognizes the role of religion and spirituality in promoting recovery for some clients.

_____Knows how to learn more about FASD intervention methods.

Skills

_____Communicates to the public the role of specialized services related to FASD prevention/intervention.

_____Identifies the "indicators" of an FASD listed in the screening policy and procedure (see Sample Policy 3).

_____Administers FASD screening and observation properly.

_____Conducts basic client education session on the relationship between substance abuse/mental health issues and FASD.

_____Conducts basic client education sessions with all female clients of childbearing age (whether pregnant or not) on the relationship between alcohol use during pregnancy and the risk of an FASD.

_____Collaborates with other team members on treatment and discharge planning.

_____Conducts a suicide risk screening.

_____Exhibits evidence-based thinking (tailoring approach to service based on clinical experience, client characteristics, knowledge of field, consultation with supervisor, constraints, and resources available).

_____Uses clinical supervision effectively.

_____Demonstrates empathic listening skills and reflection.

_____Demonstrates competency in common approaches to addressing FASD (e.g., motivational interviewing, accommodations, parent/personal navigator, coordinated care).

_____Displays confidence in ability to provide FASD-informed services.

_____Acts as a role model for a balanced, healthy lifestyle.

_____Exhibits advanced skills in dealing with resistance to change through non-confrontational approaches.

_____Identifies and responds to variations in learning styles among clients.

_____Demonstrates the ability to quickly establish a therapeutic alliance with the client: treating the client with respect, communicating a nonjudgmental attitude, listening reflectively, setting appropriate limits, being sensitive to culture and value contexts, and acting as a role model.

_____Is comfortable with and able to resolve conflict.

_____Is able to prepare clients for discharge.

Checklist 4: Characteristics and Competencies of Clinical Supervisors

Attitudes

_____Substance abuse counselors have the basic characteristics needed to provide FASD prevention/intervention.

_____Clinical supervision extends beyond talking about treatment to observing and coaching counselors directly.

Knowledge

_____Possesses all of the knowledge areas listed on Checklist 3.

_____Is knowledgeable of the role of clinical supervision.

_____Recognizes the limits and opportunities related to the role of counselors with specialized training in FASD-informed services and supports training for counselors as needed.

_____Can determine when a client who has or may have an FASD needs additional skills and services beyond the qualifications of currently-staffed counselors.

_____Is trained to screen and observe for "indicators" of an FASD.

_____Is aware of the role of transference and countertransference in the counseling and supervisory relationship.

_____Recognizes resistance to change among clinical staff and is knowledgeable of strategies to address resistance.

_____Is aware of change processes, process steps and strategies for supporting them.

_____Possesses knowledge of the FASD intervention literature and scientifically-validated intervention techniques.

Counseling Skills

_____Possesses all of the skills listed on Checklist 3.

Supervisory Skills

_____Articulates his or her approach and philosophy to clinical supervision as it relates to clinical supervision approaches described in the literature.

_____Identifies and responds to variations in learning styles among counselors.

_____Is comfortable with and able to resolve conflict among team members.

_____Models advanced counseling skills including development of therapeutic alliance, preparing clients for discharge, and dealing with client resistance.

_____Uses direct observation or taping to conduct supervisory sessions.

_____Is able to teach and model skills for providing FASD-informed services.

_____Is able to determine when referral for a formal FASD assessment is required, and facilitate such a referral.

_____Provides incentives through encouragement and support for counselors to enhance skills in providing FASD-informed services.

_____Conducts competency assessment of counselors' skills in providing FASD-informed services.

_____Shows how to learn more about FASD intervention methods.

of new knowledge, attitudes, and skills needed to help counselors and support staff address co-occurring substance use/mental health disorders and FASD prevention and intervention. The characteristics and competencies checklists presented above outline the qualifications needed at various levels or in agencies wishing to provide FASD-informed services in clients with substance use or mental disorders. However, gaps may exist; staff may be lacking in various areas and require additional training and support. In this instance, the implementation workgroup described in earlier sections may be commissioned to identify these gaps and to develop plans to provide specific training and support to individual staff members on an as-needed basis.

In addition to developing individualized plans to develop attitudes, skills, and knowledge, a number of organizational approaches can be used both to reinforce the change and to overcome resistance to change. *The Change Book* (ATTC, Second Edition 2010) offers valuable

suggestions on addressing resistance to change (particularly pp. 27–28). These include such strategies as openly discussing staff feelings related to the change, celebrating victories, promoting feedback about the change as a vehicle to improve the process, being realistic about goals, identifying and using the change leaders in promoting the change, and providing training related to the change.

Approaches to Staff Training

It is recommended that training aimed at developing the basic attitudes, knowledge, and skills for delivering FASD-informed care be provided to all agency staff as part of implementation. It is important for clinical staff to see the link between the change and organizational leadership. Thus, administrators need to attend these sessions to personally provide the vision of the organization. In addition to training current staff, it is important to consider the ways in which the organization can communicate the vision to new staff. This may be most efficiently accomplished by using existing vehicles, such as new staff orientation and training sessions and worksite orientation procedures.

Training of all clinical staff members on attitudes, knowledge, and skills specific to their positions can be conducted by administrative or clinical supervisors. Again, it is important to communicate the commitment of leadership to integrating FASD-informed services. In addition, it is recommended that training sessions provide practice in the skill areas outlined in Checklist 3. To reinforce the importance of the need to provide FASD-informed services, clinical and administrative supervisors are advised to incorporate didactic education, identification of incompatible attitudes, and coaching on the skills needed to implement the policies within existing supervision sessions and team meetings. In short, the agency's vision and commitment to addressing FASD must inform all clinical interactions between supervisors and counselors.

Figure 2.2 provides a list of recommended credentials for trainers; Appendix C, *Public and Professional Resources on FASD*, lists resources for FASD prevention and intervention training. How-To's 2.7 and 2.8 discuss the process of selecting a trainer, and how to continue the learning after the initial training is completed.

Figure 2.2
Recommended Credentials for Individuals Providing Training in FASD

- Advanced education in counseling, social work, or psychology.
- Minimum of 5 years' experience delivering substance abuse and/or mental health treatment.
- Being a qualified/experienced FASD Trainer.
- Understanding of commitment to preparing counselors to provide FASD-informed services.
- Possessing skills and experience in motivational interviewing, care coordination, and accommodations to address FASD.
- Meeting all certification or licensure qualifications and competencies for clinical supervisors.
- Knowledge of the FASD intervention literature and scientifically-validated intervention techniques.

How-To 2.7: How to Select a Trainer

Qualifications to look for in a trainer include the following:

1. Experience working with the clientele being served.
2. Ability to demonstrate the techniques as needed in role-play with staff or in-vivo (if possible).
3. Ability to address the types of challenging cases frontline staff encounter and how to work with challenging clients.
4. Understanding of the obstacles and challenges with which the frontline staff and the clinical supervisors are dealing.
5. Respectful attitude toward the clinical staff.
6. Models the principles and strategies of the intervention with the participants.
7. Ability to maintain and modify the technique for the treatment setting, willingness to review transcripts or tapes of actual sessions, and willingness to consult on the phone.
8. Willingness to accept specific training objectives to target specific staff skill sets in a case review format.
9. Knowledge of tested methods of FASD intervention and intervention literature.

See Appendix C, *Public and Professional Resources on FASD*, for links to organizations that can provide training and/or trainers. The SAMHSA FASD Center for Excellence, the National Organization on FAS (NOFAS), the Minnesota Organization on FAS (MOFAS), and the CDC's Regional Training Centers (RTCs) are good starting points.

How-To 2.8: How to Continue the Learning After the Initial Training is Completed

1. Assess the staff's knowledge, abilities, and skills with the core components of the techniques.
2. Check to see that staff continue to reframe the issues of individuals with FASD as being due (in part) to underlying neurological impairment.
3. Emphasize mastery of the underlying principles of the interventions. Always give feedback on how well staff members are doing with interventions and provide advice on simple ways to improve practice.
4. Emphasize mastery of the common techniques across approaches (e.g., motivational interviewing, case coordination, accommodations, establishing boundaries, strengths-based approaches).
5. When staff members have the basics, let them choose the approach they want to focus on next (e.g., behavioral, cognitive, beliefs, affective, family-systems, solution-focused).
6. Explore with staff members their interest in learning specific validated FASD intervention methods.

Addressing Community Relationships

How Do You Develop Referral Relationships?

Access to a range of other health and social resources is essential to quality care in substance abuse and mental health treatment settings, particularly for clients who have or may have an FASD. Agencies to which staff might refer can be screened using the following variables:

- Willing to accept referral of clients who have or may have an FASD.
- Sensitive to substance use or mental health issues.
- Able and willing to work with agencies such as ours, including regular review/ discussion of any collaborative issues.
- No or low funding impediments to working collaboratively.
- Good professional reputation in the community.
- Sufficient funding to address the needs of clients we are referring.
- Willing to cross-train with our staff.
- Existing personal relationship with the referral agency.

Also, it is preferable if certain FASD capabilities are present in any agency to which you refer:

- Individualized service planning.
- Acceptance of disability.
- Recognition of strengths.
- Incorporating individual behaviors.
- More active involvement (transportation, personally ensuring client 'hand-off,' follow up, etc.).
- Services available to child and Mom (when the FASD is intergenerational).
- Flexibility in programming (modifications will be necessary; are they willing to make them?).

How Do You Develop Relationships With the 12-Step Community?

It is useful to have the program's policy and procedures manual reflect an understanding of the essential role that 12-Step programs play in the treatment of clients with substance abuse complicated by FASD. Mental health personnel need to be sensitive and competent in integrating the principles and practices of self-help programs into the clinical process. This requires knowledge of the underlying philosophy of the 12-Step model, and an understanding of how the programs function and are structured. In like manner, counselors practicing from a 12-Step facilitation model need to appreciate how principles and practices are linked to sound counseling.

For example, the use of slogans as a form of cognitive restructuring and debate is helpful to most clients. The use of structured practices like daily meetings, sponsor contact, and reading self-help group literature can help create alternate forms of reward, relief, and life-management. The policy should recognize barriers to individuals with an FASD accessing and using 12-Step programs, including:

- Whether the individual being referred requires a navigator to help them find meetings, attend them regularly and on-time, and participate appropriately;
- Insufficient social communication and social awareness skills on the part of the individual being referred; and
- Potential exploitation of the individual by other members of the group.

How Do You Find and Use Behavioral Health Resources in the Community?

Most substance abuse and mental health programs can benefit from consulting relationships with physicians, psychologists, social workers, and other community medical, rehabilitation, social service, and mental health providers who have specialized knowledge and

resources in addressing the needs of clients who have or may have an FASD. As indicated in Part 1, Chapter 2 in the table titled *In-House FASD Assessment: An Ideal Core Team*, important professional areas to focus on in building relationships include neuropsychology and speech language pathology, occupational therapy, physical therapy, and a primary care physician.

These professionals can provide adjunct resources for such issues as difficult assessments and differential diagnosis, placement in appropriate treatment programs and/or support groups, medical management of co-occurring chronic medical conditions, specialized psychopharmacological services for clients with an FASD, discharge planning, and family services.

Finding and using these resources may be different from finding and using referral resources. Understanding the services that can be provided, fees for service, whether the service can be provided in the treatment program or whether the client must travel to a remote site, and the processes for reporting results of evaluations are some of the issues that need to be considered in using community resources. Generally, unlike referral resources, community resources will not have a formalized contract or agreement with the treatment program. Therefore, issues of confidentiality and information reporting will need to be explored.

Addressing Financial Considerations

Billing

Integration of FASD-informed services is intended to enhance treatment outcomes and, because these services are delivered by licensed and/or certified counselors who are *modifying* or offering *tailored* treatment, rather than changing the focus of treatment, such services are likely to be reimbursable under the client's primary treatment diagnosis. In this case, individual sessions that incorporate accommodations for FASD may be billed as individual counseling, psychotherapy (interactive or regular), or family therapy associated with the primary diagnosis. Organizations are advised to clarify this with state, county, federal, and private funding sources and to identify the specific procedures required to facilitate billing. Financial considerations also reinforce the need for support staff responsible for billing to understand how these services are delivered and their relationship to the primary diagnosis.

For organizations reimbursed based on case or capitated rates, reimbursement is not likely to change. Services that incorporate FASD are likely to be viewed by managed care organizations or funding agencies as value-added or optional services and thus included in established rates of reimbursement. Although incorporating FASD-informed services is not likely to increase reimbursement rates, it may improve performance on contractually mandated outcomes such as treatment engagement, retention, and effectiveness.

In their document *Operational Standards for Mental Health, Intellectual/Developmental Disabilities, and Substance Abuse Community Services Providers* (2011), the state of Mississippi has developed operational standards that can help define and inform a state reimbursement system. They are reprinted in full in Appendix H, *Operational Standards for Fetal Alcohol Spectrum Disorders (FASD): A Model*. In addition, Part 3 of this TIP, the online literature review (**http://store.samhsa.gov/home**), contains a discussion of reimbursement codes related to FASD, as well as the implications of the Patient Protection and Affordable Care Act.

Sources of Funding

Most of the costs of implementing FASD-informed services occur early in the process

of implementation, so local foundations are potential sources of funding. A one-time cost of training and knowledge dissemination to staff offers a discrete, relatively low-cost, and an attractive opportunity for local foundations to contribute to improving treatment outcomes. Applying collaboratively with other agencies demonstrates established partnerships, and should be pursued where possible. The Council on Foundations (**www.cof.org**) is an excellent starting point for identifying foundations near you and researching their missions. Other potential sources of funding include traditional state and federal grants and contracts, direct charges for services from third-party payors, and client fees for service.

Additionally, if the services provided are innovative (addressing FASD is an emerging area of care), agencies should consider partnering with social and psychological researchers at a local university to obtain research funds to support clinical efforts. Such research efforts can have many beneficial secondary effects for agency status in the community, such as developing alternative sources of funding, partnering with new groups interested in substance abuse or mental health issues in the community and/or creating learning communities, as well as providing funds for the identified project.

Addressing Continuity and Fidelity

For FASD-informed services to be fully adopted, the importance of these services will need to be consistently communicated. Policies, mission statements, program descriptions, clinical and administrative training, team meetings, and clinical supervision sessions are all useful avenues for communicating the organization's commitment to delivering FASD-informed care (see Figure 2.3). If not formally revised, these policies should at least be reviewed to ensure that they are broad enough to encompass FASD-informed services.

Implementing the Intervention With Fidelity

When implementing any intervention, it is important to identify the active elements that characterize that specific intervention. Ensuring that a new intervention is being implemented with fidelity, as distinguished from standard practice, allows administrators

Figure 2.3 Avenues for Communicating Organizational Commitment to Delivering Services to Address FASD

- Mission and vision statements
- Strategic plans
- Annual goals
- Program descriptions
- Treatment philosophy statements
- Policies and procedures
- Training sessions
- Team meetings
- Clinical supervision
- Management meetings
- Quality assurance plans
- Employee newsletters
- Electronic communication vehicles including e-mail and Intranet

to more easily determine whether the new intervention is responsible for changes in expected outcomes.

For FASD-informed care, fidelity can present challenges. Behavioral health fields are encouraged by federal agencies and funding organizations to use evidence-based approaches that have not been developed for, or accommodated to, FASD. Evidence-based approaches specifically tailored for FASD are, for now, limited, though some that have been developed and tested do have built-in fidelity monitoring mechanisms.

Fortunately, the FASD evidence base is growing rapidly. There are several scientifically validated interventions now available. There is also expert clinical consensus and publications using systematic research review and synthesis that provide support for the interventions recommended in this TIP (e.g., Adubato & Cohen, 2011).

There is also precedent for tailoring interventions. For example, the past decade has brought methods for inclusion of trauma and other co-occurring disorders into treatment provision and planning into mental health and substance abuse treatment. This could be considered 'trauma-informed' care. Established practice (e.g., cognitive behavioral therapy, or CBT) has been altered and improved by informing standard care with methods to respond to these issues (e.g., trauma-focused CBT). The strategies that have been used to modify or transform practice with these issues in mind can be used by agencies to create FASD-informed care while still maintaining fidelity of existing practices.

To create FASD-informed care and demonstrate fidelity, agencies are encouraged to:

- Access reliable FASD prevention and intervention training (training resources provided in Appendix C).
- Use this TIP and/or other manualized approaches for FASD-informed care. Suggested resources for other manualized approaches include:
  - The SAMHSA FASD Center for Excellence (primarily FASD intervention)
  - The CDC (FASD prevention and intervention approaches)
  - (**http://www.cdc.gov/ncbddd/fasd/training.html**)
- Use checklists provided in this Implementation Guide to conduct process and outcome measurement.
  - If available, use fidelity checklists for other manualized approaches for FASD-informed care (be sure that fidelity checklists describe the active elements of an intervention and define them in behavioral terms).
- Where possible, and if not cost-prohibitive, bolster use of checklist(s) with direct observation of new clinical activities.

Some issues to be solved when implementing intervention fidelity monitoring:

- Which staff members measure specific parts of the checklist(s)?
- How are results conveyed to staff?
- How does a program define an acceptable fidelity score?
- How are positive results of the efforts measured by the checklist rewarded?
- What actions need to be taken if there is poor fidelity to program elements and goals?
- How are elements of checklist(s) updated over time, and when program changes occur?

Appendix A—Bibliography

[NOTE: Part 3 of this TIP, the online Literature Review, contains its own separate reference list.]

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Appendix B—Selected Screening Instruments for Identifying Alcohol Use Among Women

[NOTE: Part 3 of this TIP, the online Literature Review, contains a full discussion of these and other alcohol screening instruments for use with women.]

T-ACE

The T-ACE is a 4-item instrument appropriate for detecting heavy alcohol use in pregnant women (Sokol, Martier, & Ager, 1989). T-ACE uses the **A**, **C**, and **E** questions from the CAGE screening tool and adds one on **T**olerance for alcohol. The first question assesses tolerance by asking if it takes more than it used to, to get "high" (i.e., intoxicated). T-ACE has sensitivity equal to the longer Michigan Alcohol Screening Test (MAST) and greater than the CAGE (Bradley, Bush, McDonell, Malone, & Fihn, 1998). It has been validated only for screening pregnant women with risky drinking (Russell, 1994).

1. How many drinks does it take for you to feel high? (**T**olerance)
2. Have people **A**nnoyed you by criticizing your drinking? A) Yes B) No
3. Have you ever felt you ought to **C**ut down on your drinking? A) Yes B) No
4. Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? (**E**ye-opener) A) Yes B) No

Scores

Any woman who answers more than two drinks on question 1 is scored 2 points. Each "yes'" to the additional 3 questions scores 1. Scoring 2 or more is considered a positive screen (Chang, Wilkins-Haug, Berman, & Goetz, 1999), and the woman should receive—or be referred to a specialist for—further assessment. At the same time, a woman could drink 2 drinks per day during pregnancy and not get a positive screen using this tool. She may not be at risk for alcoholism, but because of her pregnancy she's drinking at an unsafe level.

Sources:

- Bradley, K. A., Bush, K. R., McDonell, M. B., Malone, T., & Fihn, S. D. (1998). Screening for problem drinking: Comparison of CAGE and AUDIT. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Journal of General Internal Medicine, 13*(6), 379–388.
- Chang, G., Wilkins-Haug, L., Berman, S., & Goetz, M. A. (1999). The TWEAK: Application in a prenatal setting. *Journal of Studies on Alcohol, 60*(3), 306–309.
- Russell, M. (1994). New assessment tools for risk drinking during pregnancy: T-ACE, TWEAK, and others. *Alcohol Health and Research World, 18*(1), 55–61.
- Sokol, R. J., Martier, S. S., & Ager, J. W. (1989). The T-ACE questions: Practical prenatal detection of risk drinking. *American Journal of Obstetrics and Gynecology, 160*(4), 863-870.

TWEAK

TWEAK (Russell, Czarnecki, Cowan, McPherson, & Mudar, 1991) identifies pregnant women who are at risk for alcohol use. It consists of five items and uses a 7-point scoring system. In a study of more than 3,000 women at a prenatal clinic, the TWEAK was found to be more sensitive than the CAGE and Michigan Alcohol Screening Test (MAST), and more specific than the T-ACE (Russell et al., 1996). The tolerance question scores 2 points for an answer of three or more drinks. However, if the criterion for the tolerance question is reduced to two drinks for women, the sensitivity of TWEAK increases, and the specificity and predictive ability decrease somewhat (Chang et al., 1999).

1. (**T** – Tolerance) How many drinks does it take for you to feel high?
2. (**W** – Worried) Does your partner (or do your parents) ever worry or complain about your drinking?
   A) Yes B) No
3. (**E** – Eye-Opener) Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? (Eye-opener)
   A) Yes B) No
4. (**A** – Amnesia) Have you ever awakened the morning after some drinking the night before and found that you could not remember part of the evening before?
   A) Yes B) No
5. (**K** – K/Cut down) Have you ever felt that you ought to cut down on your drinking?
   A) Yes B) No

Scores
A woman receives 2 points on question 1 if she reports that she can hold more than 5 drinks without falling asleep or passing out. A positive response to question 2 scores 2 points, and a positive response to each of the last 3 questions scores 1 point each. A total score of 2 or more indicates that the woman is a risky drinker and requires further assessment. At the same time, drinking at any level during pregnancy is unsafe, even if the woman scores negative with this tool.

Sources:

- Chang, G., Wilkins-Haug, L., Berman, S., & Goetz, M. A. (1999). The TWEAK: Application in a prenatal setting. *Journal of Studies on Alcohol, 60*(3), 306–309.
- Russell, M., Czarnecki, D. M., Cowan, R., McPherson, E., & Mudar, P.J. (1991). Measures of maternal alcohol use as predictors of development in early childhood. *Alcoholism: Clinical & Experimental Research, 15*(6), 991–1000.
- Russell, M., Martier, S. S., Sokol, R. J., Mudar, P., Jacobson, S., & Jacobson, J. (1996). Detecting risk drinking during pregnancy: A comparison of four screening questionnaires. *American Journal of Public Health, 86*(10), 1435– 1439.

The CRAFFT Screening Interview

The CRAFFT is a behavioral health screening tool for use with children under the age of 21 and is recommended by the American Academy of Pediatrics' Committee on Substance Abuse for use with adolescents. It consists of a series of six questions developed to screen adolescents for high-risk alcohol and other drug use disorders simultaneously. It is a short, effective screening tool meant to assess whether a longer conversation about the context of use, frequency, and other risks and consequences of alcohol and other drug use is warranted. The questions should be asked exactly as written.

Begin: "I'm going to ask you a few questions that I ask all my patients. Please be honest. I will keep your answers confidential."

Part A

Appendix B—Selected Screening Instruments for Identifying Alcohol Use Among Women

During the PAST 12 MONTHS, did you:	No	Yes
1. Drink any alcohol (more than a few sips)? (Do not count sips of alcohol taken during family or religious events.)		
2. Smoke any marijuana or hashish?		
3. Use anything else to get high? ("anything else" includes illegal drugs, over the counter and prescription drugs, and things that you sniff or "huff")		
For clinic use only: Did the patient answer "yes" to any questions in Part A?		
No: Ask CAR question only, then stop.	**Yes: Ask all 6 CRAFFT questions.**	
Part B	No	Yes
1. Have you ever ridden in a CAR driven by someone (including yourself) who was "high" or had been using alcohol or drugs?		
2. Do you ever use alcohol or drugs to RELAX, feel better about yourself, or fit in?		
3. Do you ever use alcohol or drugs while you are by yourself, or ALONE?		
4. Do you ever FORGET things you did while using alcohol or drugs?		
5. Do your FAMILY or FRIENDS ever tell you that you should cut down on your drinking or drug use?		
6. Have you ever gotten into TROUBLE while you were using alcohol or drugs?		

CONFIDENTIALITY NOTICE:
The information recorded on this page may be protected by special federal confidentiality rules (42 CFR Part 2), which prohibit disclosure of this information unless authorized by specific written consent. A general authorization for release of medical information is NOT sufficient for this purpose.

Scores
Each "yes" response in Part B scores 1 point. A total score of 2 or higher is a positive screen, indicating a need for additional assessment.

Sources:

- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders, fourth edition, text revision.* Washington DC: American Psychiatric Association.
- Knight, J. R., Sherritt, L., Shrier, L. A., Harris, S. K., & Chang, G. (2002). Validity of the CRAFFT substance abuse screening test among adolescent clinic patients. *Archives of Pediatrics & Adolescent Medicine, 156*(6), 607-614.
- Knight, J. R., Shrier, L. A., Bravender, T. D., Farrell, M., Vander Bilt. J., & Shaffer, H. J. (1999). A new brief screen for adolescent substance abuse. *Archives of Pediatrics & Adolescent Medicine, 153*(6), 591-596.

AUDIT-C

The AUDIT-C comprises the first three questions of the World Health Organization (WHO) AUDIT. The AUDIT-C was first described in VA patients (Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998; Bradley et al., 2003), but has now been validated in other U.S. clinical populations (Bradley et al., 2007; Frank et al., 2008; Seale et al., 2006; Williams & Vinson, 2001).

Q1: How often did you have a drink containing alcohol in the past year?	**Points**
Never - 0 Monthly or less - 1 Two to four times a month - 2 Two to three times a week - 3 Four or more times a week - 4	
Q2: How many drinks did you have on a typical day when you were drinking in the past year?	**Points**
None, I do not drink - 0 1 or 2 - 0 3 or 4 - 1 5 or 6 - 2 7 to 9 - 3 10 or more - 4	
Q3: How often did you have six or more drinks on one occasion in the past year?	**Points**
Never - 0 Less than monthly - 1 Monthly - 2 Weekly - 3 Daily or almost daily - 4	

Scores
The AUDIT-C is scored on a scale of 0–12 (scores of 0 reflect no alcohol use). In women, a score of 3 or more is considered positive.

Sources:

- Bradley, K. A., Bush, K. R., Epler, A. J., Dobie, D. J., Davis, T. M., Sporleder, J. L., Maynard, C., Burman, M. L., & Kivlahan, D. R. (2003). Two brief alcohol-screening tests From the Alcohol Use Disorders Identification Test (AUDIT): Validation in a female Veterans Affairs patient population. *Archives of Internal Medicine, 163*(7), 821-829.
- Bradley, K. A., DeBenedetti. A. F., Volk, R. J., Williams, E. C., Frank, D., & Kivlahan, D. R. (2007). AUDIT-C as a brief screen for alcohol misuse in primary care. *Alcoholism: Clinical and Experimental Research, 31*(7), 1-10.
- Bush, K., Kivlahan, D. R., McDonell, M. B., Fihn, S. D., & Bradley, K. A. (1998). The AUDIT alcohol consumption questions (AUDIT-C): An effective brief screening test for problem drinking. *Archives of Internal Medicine, 158*(16), 1789-195.
- Frank, D., Debenedetti, A. F., Volk, R. J., Williams, E. C., Kivlahan, D. R., & Bradley, K. A. (2008). Effectiveness of the AUDIT-C as a screening test for alcohol misuse in three racial/ethnic groups. *Journal of General Internal Medicine, 23*(6), 781-787.
- Seale, J. P., Boltri, J. M., Shellenberger, S., Velasquez, M. M., Cornelius, M., Guyinn, M., Okosun, I., & Sumner, H. (2006). Primary care validation of a single screening question for drinkers. *Journal of Studies on Alcohol and Drugs, 67*(5), 778-784.
- Williams, R., & Vinson, D. C. (2001). Validation of a single screening question for problem drinking. *The Journal of Family Practice, 50*(4), 307-312.

Appendix C—Public and Professional Resources on FASD

The SAMHSA FASD Center for Excellence

SAMHSA FASD Center for Excellence
www.fasdcenter.samhsa.gov

The official site of the SAMHSA FASD Center for Excellence provides information and resources about FASD, as well as awareness materials, a fully searchable database, and access to training, technical assistance, and conference/event speakers.

National Association of FASD State Coordinators
http://fasdcenter.samhsa.gov/statesystemsofcare/nafsc.aspx

The SAMHSA FASD Center for Excellence helped to establish the National Association of FASD State Coordinators (NAFSC) in 2003 to support state-based efforts to increase the system of care available to individuals with an FASD and their families. NAFSC's mission is to promote prevention, treatment, and care systems for FASD, nationwide, through collaboration with systems within their respective states and among member states. The site provides updates on current activities, a roster of current members, and full contact information.

Assessment and Diagnosis

National Organization on FAS (NOFAS)
www.nofas.org

NOFAS is a leading voice and resource for the FASD community, and was one of the first. Founded in 1990, NOFAS is still the only international non-profit organization committed solely to FASD primary prevention, advocacy, and support. NOFAS has 30 affiliate programs around the country, and provides a Resource Directory to help locate FASD-related services. Also see *Information and Training*, below.

University of Washington: FAS Diagnostic & Prevention Network
http://depts.washington.edu/fasdpn/

The Washington State FAS Diagnostic & Prevention Network (FAS/DPN) is a network of four WA State community-based interdisciplinary FASD diagnostic clinics linked by the core clinical/research/training clinic at the Center on Human Development and Disability at the University of Washington in Seattle. The network was established in 1993. Each clinic in the network uses the same interdisciplinary approach to diagnosis and the same systematic diagnostic method; the *4-Digit Diagnostic Code*. The mission of the FAS DPN is primary and secondary prevention of FAS through screening, diagnosis, intervention, training, education, and research. The FAS DPN began diagnosing patients in 1993, and has diagnosed over 2,000 patients to date. See also *Information and Training*, below.

Grant Opportunities

SAMHSA Grant Opportunities
http://www.samhsa.gov/grants/

SAMHSA's grant management site allows applicants and prospective applicants to review Requests for Application (RFA's) from each of SAMHSA's sub-agencies, submit applications online, track application status, review reporting requirements, and manage the activity of awarded grants.

Grants.gov
www.grants.gov

Grants.gov was established as a governmental resource named the E-Grants Initiative, part of the President's 2002 Fiscal Year Management Agenda to improve government services to the public. Today, Grants.gov is a central storehouse for information on over 1,000 grant programs and provides access to approximately $500 billion in annual awards. The site is searchable by agency, keyword, and a variety of other variables.

Information and Training

Families Moving Forward
http://depts.washington.edu/fmffasd/

The *Families Moving Forward Program* intervention is a scientifically validated behavioral consultation program tailored for families raising preschool and school-aged individuals with FASD or confirmed prenatal alcohol exposure. The intervention includes methods and materials that appropriately trained counselors can use when working with families of a client who has an FASD. Training on FASD intervention, and on the *Families Moving Forward Program*, is regularly available through the East Coast (Florida) or West Coast (Seattle) training centers, or on-site at an agency location in the United States, Canada, or elsewhere. Once training is completed, all materials are freely available on a Web site to be downloaded.

The FASD Information Page of the Centers for Disease Control and Prevention (CDC)
http://www.cdc.gov/ncbddd/fasd/

The CDC's FASD page offers extensive information on the background of FASD, diagnosis and treatment, and training and educational materials, as well as access to articles, print materials, and multimedia tools for raising awareness.

FASD Regional Training Centers
http://www.cdc.gov/ncbddd/fasd/index.html

The CDC's FASD Regional Training Centers (RTCs) develop, implement, and evaluate educational curricula regarding FASD prevention, identification, and care, and incorporate the curricula into training programs at each grantee's university or college, into other schools throughout their regions, and into the credentialing requirements of professional boards. Check the site for links to specific, currently-active regional sites. Currently funded regional sites include the following:

- **Southeastern FASD Regional Training Center**
- **Arctic FASD Regional Training Center**
- **Frontier FASD Regional Training Center**

The National Institute on Alcohol Abuse and Alcoholism
http://www.niaaa.nih.gov

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) is one of the 27 Institutes and Centers that comprise the National Institutes of Health (NIH), a component of HHS. NIAAA is the primary U.S. agency for conducting and supporting research on the causes, consequences, prevention, and treatment of alcohol abuse, alcoholism, and alcohol problems, including health effects such as FASD. NIAAA disseminates research findings to general, professional, and academic audiences. The Web site has links to relevant NIAAA publications. The FASD-specific **Web link** at NIAAA is **http://www.niaaa.nih.gov/research/major-initiatives/fetal-alcohol-spectrum-disorders**. This page also links to overviews of the activities of NIAAA's Interagency Coordinating Committee on FASD (ICCFASD).

National Organization on FAS (NOFAS)
www.nofas.org

NOFAS is a leading voice and resource for the FASD community, and was one of the first. Founded in 1990, NOFAS is still the only international non-profit organization committed solely to FASD primary prevention, advocacy, and support. The official site provides access to materials for educators, healthcare professionals, expectant mothers, and individuals and families living with an FASD. Also see *Assessment and Diagnosis*, above.

University of Washington FAS/DPN Training
http://depts.washington.edu/fasdpn/htmls/training.htm

In addition to assessment and diagnostic services, the University of Washington's FAS/DPN offers 1-day trainings on screening, diagnosis, treatment planning, and primary prevention of FASD, and also 2-day and online trainings for interdisciplinary clinical teams (or individual clinical team members) seeking to establish a FASD Diagnostic Clinic in their community.

Research and Journal Articles

Appendix A of this TIP contains an extensive bibliography for further reading on FASD, and Part 3 of this TIP, the online Literature Review (**http://store.samhsa.gov/home**), contains its own bibliography. In addition, the following Web sites and journals are excellent resources for further literature on FASD and related issues.

Alcohol
http://www.sciencedirect.com/science/journal/07418329/44/7-8

In 2010, the journal *Alcohol* published two issues devoted entirely to FASD diagnosis and intervention (Volume 44, issues 7-8). Together, these issues contain 16 articles, all of which can be accessed via the link above. Note: There is a cost for each article.

The Collaborative Initiative on FASD (CIFASD)
http://cifasd.org/

The Collaborative Initiative on FASD (CIFASD) is a consortium dedicated to informing and developing effective interventions and treatment approaches for FASD through multidisciplinary research involving basic, behavioral, and clinical investigators and projects. The Web site contains an extensive bibliography of recent FASD-related literature (2004 to the present). Many of the bibliographic items link to full abstracts through PubMed, but full articles must be purchased.

The Journal of Psychiatry & Law
http://www.federallegalpublications.com/journal-of-psychiatry-law/

The Winter 2010 (**Volume 38, issue 4**) and Spring 2011 (**Volume 39, issue 1**) issues of *The Journal of Psychiatry & Law* are devoted entirely to FASD-related issues, ranging from intervention approaches, to addressing FASD in the criminal justice system, to FASD as an adoption disclosure issue. A full listing of the articles is contained at the Volume links above. Note: There is a cost for each full issue.

Research Search Engines

Both the SAMHSA FASD Center for Excellence and NOFAS offer free online search engines that can be used to access FASD-related literature by author, title, keywords, or topic area.

Support Networks for Individuals with an FASD and Their Families

Birth Mothers Network
http://www.nofas.org/join-the-circle-of-hope/

The Birth Mothers Network, also known as the Circle of Hope, was founded through NOFAS in 2004. It is a network of women who have consumed alcohol during pregnancy and may have a child or children with an FASD. Members are lovingly referred to as "Warrior Moms" because of their incredible strengths. Many of the women are in recovery from alcoholism, or alcohol and drug addiction. However, the network also includes women without the disease of addiction, but who drank alcohol during pregnancy. The women of the Birth Mothers Network serve as mentors to one another, help each other cope with the challenges of parenting a child with an FASD, and provide caring, non-judgmental support to members who are in recovery.

Living With FASD
http://www.nofas.org/living

The Living With FASD page is provided by NOFAS, and contains links to financial assistance programs such as Supplemental Security Income (SSI) and Social Security Disability Insurance (SSDI) (both can be contacted at 1-800-772-1213), and Medicaid, as well as family and mother support programs such as **Women, Infants and Children** (WIC).

Additional Support Sites

In addition to research and general information, each of the following sites provides access to other members of the FASD community, as well as parenting guidance, personal stories from others who are coping with FASD, and guides to services.

- The FAS Community Resource Center

http://www.come-over.to/FASCRC/

- FASlink

http://www.faslink.org/

- One-Stop Centers

http://www.careeronestop.org/

One-Stop Centers are Internet job sites that can provide links to your state Department of Labor and Workforce Development, the local division for vocational rehabilitation services, and/or specific state initiatives for development of customized employment for people with disabilities.

Appendix D—The FASD 4-Digit Code Caregiver Interview Checklist: Profiles of FASD

The form below was developed by the Washington State FAS Diagnostic and Prevention Network (FAS DPN), and is part of the *4-Digit Diagnostic Code* (Astley, 2004). The caregivers of all patients receiving an FASD diagnostic evaluation in the Washington State FAS DPN clinics participate in a 2-hour interview with the pediatrician and psychologist. The purpose of the interview is to identify areas of significant delay/impairment across a wide array of functional domains.

The article *Profile of the First 1,400 Patients Receiving Diagnostic Evaluations for Fetal Alcohol Spectrum Disorder at the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network*, by Dr. Susan Astley (2010), provides a graphical summary of the first 1,400 caregiver interviews conducted by the FAS DPN clinics. Presented is the proportion of patients classified by the pediatrician as "significantly delayed/impaired" in behaviors addressed in a 2-hour, structured caregiver interview administered jointly by the pediatrician and psychologist during the FASD diagnostic evaluation. This graphical presenta-tion illustrates the cumulative increase in impairment as one advances across the FASD diagnostic groups. The illustration is color-dependent and too complex to present in this TIP. However, readers are encouraged to access the article at the following link: **http://depts.washington.edu/fasdpn/pdfs/astley-profile-2010.pdf**

The FASD 4-Digit Code Caregiver Interview Checklist

Severity Score: Severity of Delay/Impairment (Displayed along left margin)

Circle: **0** = Unknown, Not Assessed, Too Young **1** = Within Normal Limits **2** = Mild to Moderate **3** = Significant

Severity	Caregiver Observations
	Planning/Temporal Skills
0 1 2 3	Needs considerable help organizing daily tasks _____
0 1 2 3	Cannot organize time _____
0 1 2 3	Does not understand concept of time _____
0 1 2 3	Difficulty in carrying out multi-step tasks _____
0 1 2 3	Other _____

Appendix D—The FASD 4-Digit Code Caregiver Interview Checklist: Profiles of FASD

	Behavioral Regulation/Sensory Motor Integration
0 1 2 3	Poor management of anger/tantrums _____
0 1 2 3	Mood swings _____
0 1 2 3	Impulsive _____
0 1 2 3	Compulsive _____
0 1 2 3	Perseverative _____
0 1 2 3	Inattentive _____
0 1 2 3	Inappropriately [high or low] activity level _____
0 1 2 3	Lying/stealing _____
0 1 2 3	Unusual [high or low] reactivity to [sound touch light] _____
0 1 2 3	Other _____
	Abstract Thinking/Judgment
0 1 2 3	Poor judgment _____
0 1 2 3	Cannot be left alone _____
0 1 2 3	Concrete, unable to think abstractly _____
0 1 2 3	Other _____
	Memory/Learning/Information Processing
0 1 2 3	Poor memory, inconsistent retrieval of learned information _____
0 1 2 3	Slow to learn new skills _____
0 1 2 3	Does not seem to learn from past experiences _____
0 1 2 3	Problems recognizing consequences of actions _____
0 1 2 3	Problems with information processing speed and accuracy _____
0 1 2 3	Other _____
	Spatial Skills and Spatial Memory
0 1 2 3	Gets lost easily, has difficulty navigating from point A to point B _____
0 1 2 3	Other _____
	Social Skills and Adaptive Behavior
0 1 2 3	Behaves at a level notably younger than chronological age _____
0 1 2 3	Poor social/adaptive skills _____
0 1 2 3	Other _____
	Motor/Oral Motor Control
0 1 2 3	Poor/delayed motor skills _____
0 1 2 3	Poor balance _____
0 1 2 3	Other _____

Source: Astley, S. J. (2004). *Diagnostic guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code*, Third Edition. Seattle, WA: University of Washington. Accessed June 1, 2012 at **http://depts.washington.edu/fasdpn/pdfs/FASD-2004-Diag-Form-08-06-04.pdf**. Used with permission from the author.

Appendix E—Comparison of Current FASD Diagnostic Systems

Fetal Alcohol Syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. Almost four decades have passed since the term FAS was first coined. The condition is now recognized as a spectrum of disorders: Fetal Alcohol Spectrum Disorders (FASD). Substantial progress has been made in developing specific criteria for delineating diagnoses under the umbrella of FASD. In the 14 years since the publication of the seminal report on FAS by the Institute of Medicine in 1996, clear consensus has been reached on two fundamental issues: 1) an FASD diagnostic evaluation is best conducted by a team of professionals from multiple disciplines (medicine, psychology, speech-language, occupational therapy) and 2) the team should use rigorously case-defined and validated FASD diagnostic guidelines.

In 2011, Dr. Susan Astley wrote a chapter on Diagnosing FASD in a book entitled *Prenatal Alcohol Use and Fetal Alcohol Spectrum Disorders: Diagnosis, Assessment and New Directions in Research and Multimodal Treatment* (Astley, 2011). This chapter provided a brief overview of the discovery of FASD, diagnostic challenges, how diagnostic guidelines and clinical models have evolved over time to address these challenges, and how new technology may influence the future of FASD diagnosis. The tables below come from that chapter, and provide a side-by-side comparison of the five most commonly used diagnostic guidelines for forms of FASD; the 4-Digit Diagnostic Code (Astley, 2004b), the guidelines developed by the Centers for Disease Control and Prevention (Bertrand et al., 2004), the Canadian guidelines (Chudley et al., 2005), the revised guidelines of the Institute of Medicine (IOM) (Hoyme et al., 2005), and the original IOM guidelines (Stratton et al., 1996). Table 1 compares diagnostic criteria for FAS; Table 2, pFAS; Table 3, ARND; and Table 4, ARBD. These tables are reprinted here with the permission of the author.

It is important to note that, for the purposes of this Appendix, the 4-Digit Diagnostic Code has been translated, as best as possible, into a text (rather than numeric) format. This was done to facilitate comparison to the other guidelines that publish their diagnostic criteria in text format. Diagnostic teams should not use the textual translations of the 4-Digit Code presented in Tables 1-4 to derive a 4-Digit Code, but rather the numeric format presented in the *Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code*, Third Edition (Astley, 2004a).

Table 1. FAS Diagnostic Criteria: Comparison Across the Five Most Current FASD Diagnostic Guidelines

	4-Digit Code (2004)	CDC (2004)	Canadian (2005)	Revised IOM (2005)	IOM (1996)
Growth	Prenatal and/ or postnatal height or weight < 10th percentile (Growth Ranks 2-4)	Prenatal and/ or postnatal height or weight < 10th percentile	At least 1 of the following: • Prenatal and/ or postnatal height or weight < 10th percentile • Weight-to-height ratio (<10th percentile)	Prenatal and/ or postnatal height or weight < 10th percentile	At least 1 of the following: • Low birth weight • Low weight for height • Decelerating weight
Face	All 3 of the following at any age: • PFL < 3rd percentile • Smooth philtrum Rank 4 or 5 • Thin upper lip Rank 4 or 5 (Face Rank 4)	All 3 of the following: • PFL < 10th percentile • Smooth philtrum Rank 4 or 5 • Thin upper lip Rank 4 or 5	All 3 of the following at any age: • PFL < 3rd percentile • Smooth philtrum Rank 4 or 5 • Thin upper lip Rank 4 or 5	2 or more of the following: • PFL < 10th percentile • Smooth philtrum Rank 4 or 5 • Thin upper lip Rank 4 or 5	Characteristic pattern that includes features such as short PFL, flat upper lip, flattened philtrum, and flat midface.
CNS	At least 1 of the following: • Structural/ Neurological: (e.g., OFC < 3rd percentile, abnormal structure, seizure disorder, hard signs) • Severe Dysfunction: (3 or more domainsa of function with impairment 2 or more SDs below the mean)	At least 1 of the following: • Structural/ Neurological: (e.g., OFC < 10th percentile, abnormal structure, seizure disorder, hard/soft signs) • Dysfunction[b]: • 3 or more domains of function with impairment 1 or more	At least 3 of the following Structure/ Neurological/ Functional domains with impairment[c]: • Hard/ soft signs, structure, cognition, communi-cation, academic achievement, memory, executive functioning, abstract reasoning, ADD,	At least 1 of the following: • Structural • OFC < 10th percentile • Abnormal structure	At least 1 of the following: • Structural/ Neurological: • Decreased cranial size at birth • Abnormal structure (e.g., microcephaly, partial/ complete agenesis of the corpus callosum, cerebellar hypoplasia) • Neurological hard/soft signs

	(CNS Rank 3 and/or 4)	SDs below the mean • Global deficit (2 or more SDs below the mean)	adaptive behavior, social skills, or communi-cation		
Alcohol	Confirmed or Unknown (Alcohol Ranks 2,3 or 4)	Confirmed or Unknown	Confirmed or Unknown	Confirmed-excessive or Unknown	Confirmed-excessive or Unknown

a. 4-Digit Code: Domains may include, but are not limited to: executive function, memory, cognition, social/adaptive skills, academic achievement, language, motor, attention, or activity level.
b. CDC: Performance substantially below that expected for an individual's age, schooling, or circumstances, as evidenced by: 1) Global cognitive or intellectual deficits representing multiple domains of deficit (or significant developmental delay in younger children) with performance below the 3rd percentile (2 standard deviations below the mean for standardized testing) or 2) Functional deficits below the 16th percentile (1 standard deviation below the mean for standardized testing) in at least three of the following domains: a) cognitive or developmental deficits or discrepancies b) executive functioning deficits c) motor functioning delays d) problems with attention or hyperactivity e) social skills f) other, such as sensory problems, pragmatic language problems, memory deficits, etc.
c. Canadian: Impairment indicates scores $\geq$ 2 SDs below the mean, discrepancies of 1.5-2 SDs among subtests, or $\geq$ 1 SD discrepancy between subdomains.

Table 2: Partial FAS Diagnostic Criteria: Comparison Across the Five Most Current FASD Diagnostic Guidelines

	4-Digit Code (1997-2004)	CDC[a] (2004)	Canadian (2005)	Revised IOM (2005)	IOM (1996)
Growth	Prenatal or postnatal height or weight < 10th percentile (Growth Ranks 1-4)	--	No growth deficiency	Prenatal and/or postnatal height or weight < 10th percentile	At least 1 of the following: • Low birth weight • Low weight for height • Decelerating weight
Face	All 3 of the following at any age: • PFL < 3rd percentile	--	2 of the following at any age: • PFL < 3rd percentile	2 or more of the following: • PFL < 10th percentile	Some components of the pattern of FAS characteristic facial anomalies.

Appendix E— Comparison of Current FASD Diagnostic Systems

	• Smooth philtrum Rank 4 or 5 • Thin upper lip Rank 4 or 5 (Face Ranks 3 or 4)*		• Smooth philtrum Rank 4 or 5 • Thin upper lip Rank 4 or 5	• Smooth philtrum Rank 4 or 5 • Thin upper lip • Rank 4 or 5	
CNS	At least 1 of the following: • Structural/ Neurological: (e.g., OFC < 3rd percentile, abnormal structure, seizure disorder, hard signs) • Severe Dysfunction: (3 or more domains[b] of function with impairment 2 or more SDs below the mean) (CNS Rank 3 and/or 4)	--	At least 3 of the following Structure/ Neurological/ Functional domains with significant impairment[c]: • Hard/soft signs, structure, cognition, communication, academic achievement, memory, executive functioning, abstract reasoning, ADD, adaptive behavior, social skills, or communication	At least 1 of the following: • Structural • OFC < 10th percentile • Abnormal structure • Dysfunction • Complex pattern[d] of behavior/ cognitive abnorm-alities	At least 1 of the following: • Structural/ Neurological: • Decreased cranial size at birth • Abnormal structure • Hard/soft signs • Dysfunction • Complex pattern[e] of behavior/ cognitive abnormalities
Additional Criteria	PFAS requires the CNS and Alcohol criteria to be met and allows either the Growth or the Face criteria to be relaxed just slightly. • *If the growth deficiency criteria above are met, one facial feature may be relaxed as follows: (PFL < 1 SD, or Philtrum Rank 3, or Lip Rank 3) or	--	None	PFAS requires the Face and Alcohol criteria to be met and only one of the following additional criteria: • Growth • CNS Structural • CNS dysfunction	PFAS requires the Face and Alcohol criteria to be met and only one of the following additional criteria: • Growth • CNS Structural/ Neurological • CNS dysfunction

	• If the FAS face criteria are met, growth can be relaxed to normal.				
Alcohol	Confirmed (Alcohol Ranks 3 or 4)	--	Confirmed	Confirmed-excessive or Unknown	Confirmed-excessive

a. The CDC Guidelines only address FAS.
b. 4-Digit Code: Domains may include, but are not limited to: executive function, memory, cognition, social/adaptive skills, academic achievement, language, motor, attention, or activity level.
c. Canadian: Impairment indicates scores ≥ 2 SDs below the mean, discrepancies of 1.5 to 2 SDs among subtests, or ≥ 1 SD discrepancy between subdomains.
d. Hoyme: Marked impairment in the performance of complex tasks (complex problem solving, planning, judgment, abstraction, metacognition, and arithmetic tasks); higher-level receptive and expressive language deficits; and disordered behavior (difficulties in personal manner, emotional lability, motor dysfunction, poor academic performance, and deficient social interaction).
e. IOM: Complex pattern of behavior or cognitive abnormalities that are inconsistent with developmental level and cannot be explained by familial background or environment alone: e.g., learning difficulties; deficits in school performance; poor impulse control; problems in social perception; deficits in higher level receptive and expressive language; poor capacity for abstraction or metacognition; specific deficits in mathematical skills; or problems in memory, attention or judgment.

Table 3. ARND (or its equivalent: Static Encephalopathy/Alcohol Exposed or Neurobehavioral Disorder/Alcohol Exposed) Diagnostic Criteria: Comparison Across the Five Most Current FASD Diagnostic Guidelines

	4-Digit Code (1997-2004)	CDC[a] (2004)	Canadian (2005)	Revised IOM (2005)	IOM (1996)
Growth	Normal to deficient (Growth Ranks 1-4)	--	No growth deficiency	No growth deficiency	No growth deficiency
Face	No more than 1 of the following: • PFL < 3rd percentile • Philtrum Rank 4 or 5 • Lip Rank 4 or 5 (Face Ranks 1-2)	--	No FAS facial phenotype	No FAS facial phenotype	Presumably no components of the pattern of FAS characteristic facial anomalies.

Appendix E— Comparison of Current FASD Diagnostic Systems

CNS	Criteria_ for "Static_ Encephalopathy" At least 1 of the following: • Structural/ Neurological: (e.g., OFC < 3rd percentile, abnormal structure, seizure disorder, hard signs) • Severe Dysfunction: (3 or more domains[b] of function with impairment 2 or more SDs below the mean) (CNS Rank 3 and/or 4) Criteria for_ "Neurobehavioral Disorder"[c] • No Structural/ Neurological abnormalities. • Moderate Dysfunction: 1-2 domains[b] of function with impairment > 1.5 SDs below the mean)	--	At least 3 of the following Structure/ Neurological/ Functional domains with significant impairment[c]: • Hard/soft signs, structure, cognition, communication, academic achievement, memory, executive functioning, abstract reasoning, ADD, adaptive behavior, social skills, or communication	At least 1 of the following: • Structural • OFC < 10th percentile • Abnormal structure • Dysfunction • Complex pattern[d] of behavior/ cognitive abnormalities	At least 1 of the following: • Structural/ Neurological: • Decreased cranial size at birth • Abnormal structure • Hard/soft signs • Dysfunction • Complex pattern[e] of behavior/cognitive abnormalities
Additional Criteria	The term ARND is not used. The following terms are used in lieu of ARND: Static Encephalopathy (Severe dysfunction) Neurobehavioral Disorder	--	--	--	--

	(Moderate dysfunction)				
Alcohol	Confirmed (Alcohol Ranks 3 or 4)	--	Confirmed	Confirmed-excessive	Confirmed-excessive

a. The CDC Guidelines only address FAS.
b. 4-Digit Code: Domains may include, but are not limited to: executive function, memory, cognition, social/adaptive skills, academic achievement, language, motor, attention, or activity level. MRI research confirms Neurobehavioral Disorder/Alcohol Exposed is a distinct, clinically meaningful subclassification under the umbrella of FASD [6].
c. Canadian: Impairment indicates scores ≥ 2 SDs below the mean, discrepancies of 1.5-2 SDs among subtests, or ≥ 1 SD discrepancy between subdomains.
d. Hoyme: Marked impairment in the performance of complex tasks (complex problem solving, planning, judgment, abstraction, metacognition, and arithmetic tasks); higher-level receptive and expressive language deficits; and disordered behavior (difficulties in personal manner, emotional lability, motor dysfunction, poor academic performance, and deficient social interaction).
e. IOM: Complex pattern of behavior or cognitive abnormalities that are inconsistent with developmental level and cannot be explained by familial background or environment alone: e.g., learning difficulties; deficits in school performance; poor impulse control; problems in social perception; deficits in higher level receptive and expressive language; poor capacity for abstraction or metacognition; specific deficits in mathematical skills; or problems in memory, attention or judgment.

Table 4. ARBD Diagnostic Criteria: Comparison Across the Five Most Current FASD Diagnostic Guidelines

	4-Digit Code[a] (1997-2004)	CDC[b] (2004)	Canadian[a] (2005)	Revised IOM (2005)	IOM (1996)
Growth	--	--	--	Not specified	Not specified
Face	--	--	--	2 or more of the following: • PFL < 10th percentile • Philtrum Rank 4 or 5 • Lip Rank 4 or 5	Not specified
CNS	--	--	--	Not specified	Not specified

Appendix E— Comparison of Current FASD Diagnostic Systems

Congenital Defects	--	--	--	1 or more of the following: • Cardiac: Atrial septal defects, Ventricular septal defects, Aberrant great vessels, Tetralogy of Fallot. • Skeletal: Hypoplastic nails, Shortened fifth digits, Radioulnar synostosis, Flexion contractures, Camptodactyly, Clinodactyly, Pectus excavatum and carinatum, Klippel-Feil syndrome, Hemivertebrae, Scoliosis. • Renal: Aplastic/dysplastic/hypoplastic kidneys, Horseshoe kidneys, Ureteral duplications, Hydronephrosis. • Ocular: Strabismus, Retinal vascular anomalies, Refractive problems secondary to small globes. • Auditory: Conductive hearing loss, Neurosensory hearing loss. • Other: Virtually every malformation has been described in some patient with FAS.	Congenital structural defects in 1 of the following categories, including malformations and dysplasias (if the patient displays minor anomalies only, 2 must be present): • Cardiac: Atrial septal defects, Ventricular septal defects, Aberrant great vessels, conotruncal heart defects. • Skeletal: Radioulnar synostosis, Vertebral segmentation defects, Large joint contractures, Scoliosis. • Renal: Aplastic/dysplastic/hypoplastic kidneys, "Horseshoe" kidney/ureteral duplications. • Eyes: Strabismus, Ptosis, Retinal vascular anomalies, Optic nerve hypoplasia. • Ears: Conductive hearing loss, Neurosensory hearing loss. • Minor Anomalies: Hypoplastic nails, Short fifth digits, Clinodactyly of fifth fingers, Pectus carinatum/excavatum, Camptodactyly, "Hockey stick" palmar creases, Refractive errors,

	--	--	--	The etiologic specificity of most of these anomalies to alcohol teratogenesis remains uncertain.	"Railroad track" ears.
Alcohol	--	--	--	Confirmed-excessive	Confirmed-excessive

a. The 4-Digit Code and Canadian Guidelines do not recognize ARBD as a FASD diagnostic classification.
b. The CDC Guidelines only address FAS.

Appendix F—Sample Crisis/ Safety Plan

The following is a suggested Crisis/Safety Plan that can be used with a client who has or may have an FASD, or with a family member or caregiver of the client. The plan is designed to help identify safety concerns for the client, actions that can be taken to prevent or address those concerns, and support persons that can assist.

If you have access to an electronic version of this TIP, consider printing this and the following page back-to-back as a way to reproduce the form for your use. This form has been adapted from materials in the *Families Moving Forward Program* (**http://depts.washington.edu/fmffasd/**). Check their Web site for additional resources.

Client Crisis/Safety Plan

Client's Name: _____ Date: _____

Caregiver(s): _____

Legal Guardian(s): _____

Provider/Counselor: _____

1. List the crisis or safety concerns for the client and other family members/ caregivers.

_____

_____

_____

_____

☐ *No crisis or safety concerns were identified. Clients were given appropriate resources. Item #2 below was filled out.*

2. List formal and informal supports. These can be family, friends, respite providers, social workers, community supports such as faith-based organizations (and so on). These are people available to help with crisis/ safety concerns. *(Fill out even if there are no current concerns.)*

_____

_____

_____

3. How can these support people help during a crisis?

Name: _____ Phone: _____

Action: _____

_____

Name: _____ Phone: _____

Action: _____

_____

Name: _____ Phone: _____

Action: _____

_____

Name: _____ Phone: _____

Action: _____

_____

4. Steps for the crisis plan. *(Use if safety concerns are immediate or the situation could get out of hand. Describe what might happen and what you'd do. Include phone numbers of people you would call.)*

_____

_____

_____

IF THERE IS A MEDICAL EMERGENCY, CALL 911.

5. Local Crisis Line number: _____

This is only a suggested action plan. Input from other service providers should be taken into account. This can include therapists, doctors, and emergency services.

This sample Crisis/Safety Plan was developed as part of the *Families Moving Forward Program* and adapted for this TIP with permission of the authors.

Appendix G—Services and Supports Checklist

Counselors can provide invaluable assistance to the family/caregivers of an individual who has or may have an FASD, or to their client with FASD, by helping them access appropriate services and supports. Below is a comprehensive checklist that can help a counselor and client identify what supports are needed, and choose what community resources are realistic as linkages.

If you have access to an electronic version of the TIP, consider printing this and the following page back-to-back to use with clients as an efficient worksheet. This form has been adapted from materials in the *Families Moving Forward Program* (**http://depts.washington.edu/fmffasd**). Check their Web site for more resources.

Services and Supports Checklist

Client's Name: _____ Date: _____

Which of the following would you like to look into?

Material and Financial Assistance and Resources

_____Government/financial assistance (SSI, WIC, etc.)
_____Low-cost housing
_____Adoption funding
_____Developmental disabilities funding

Information and Advocacy Resources

_____Advocacy services
_____Case management services
_____Diagnostic and evaluation services (FASD/non-FASD)
_____Guardian/future planning services
_____Information and referral services
_____Parent/family training, parenting classes
_____Legal services/assistance

Health and Mental Health Resources

_____Health/mental health care financial support
_____Medication evaluation

_____Mental health services
_____Alcohol and drug treatment/recovery programs
_____Family planning/contraceptive resources
_____Substance abuse education for children

Childcare and Respite Resources
_____In-home respite/sitter services
_____Out-of-home respite services
_____Daycare

Crisis Lines and Response Teams
_____Crisis lines/response teams
_____Crisis response teams
_____Child protective services
_____Other crisis resources

Mentor and Support Groups and Resources
_____FASD caregiver/family support groups
_____FASD self-advocacy resources
_____Birth mother network
_____Other types of support groups
_____Sibling support groups
_____Parent-to-parent support (formal and informal)
_____Mentor programs
_____Recreational activities
_____Recovery supports
_____Other support resources

Educational Services and Job Resources
_____Special education and other accommodation programs
_____School-based treatment/therapeutic services
_____Behavior management assistance
_____Tutoring
_____Educational advocacy services
_____Vocational rehabilitation
_____Vocational or job counseling/coaching

Internet and Educational Resources
_____Information on FASD and FASD supports
_____E-mail lists (for? _____)
_____Internet sites (about? _____)
_____Other brochures, books (about? _____)

OTHER
_____Juvenile justice services
_____Representative (or protective) payee services
_____ _____

This checklist was developed as part of the *Families Moving Forward Program*, and is adapted for this TIP with permission of the authors.

Appendix H—Operational Standards for Fetal Alcohol Spectrum Disorders (FASD): A Model

The state of Mississippi has developed operational standards addressing FASD that can potentially help define and inform other state reimbursement systems. The following selected standards are taken from the Mississippi Department of Mental Health's *Operational Standards for Mental Health, Intellectual/ Developmental Disabilities, and Substance Abuse Community Service Providers*, published January 2011.

- **XVI.D.1.** Fetal alcohol spectrum disorders (FASD) is an umbrella term describing the range of effects that can occur in an individual whose mother drank alcohol during pregnancy. These effects may include physical, mental, behavioral, and/or learning disabilities with possible lifelong implications. Behavioral or cognitive problems may include intellectual disability, learning disabilities, attention deficits, hyperactivity, poor impulse control, and social, language, and memory deficits. FASD occurs in about 1% of all live births, or about 450 to 500 new cases in Mississippi per year. The damage caused by prenatal alcohol exposure is permanent. The effects cannot be reversed, but many of them can be treated with the appropriate combination of interventions and support. Secondary disabilities of FASD include mental health issues (90%), school problems (60%), trouble with the law (60%) and attempted suicide (23%). Early identification and diagnosis of children with an FASD can help ensure appropriate treatment which in turn will help reduce the occurrence and impact of these secondary disabilities.
- **XVI.D.2.** Children ages birth to age 18 must be screened within six (6) months of Intake to determine if there is a need for a Fetal Alcohol Spectrum Disorders (FASD) diagnostic evaluation. Youth ages 18 to 24 may be screened for an FASD if the provider has reason to believe that there was prenatal alcohol exposure.
- **XVI.D.3.** The FASD screening tool1 will be provided by the Division of Children and Youth Services (see the DMH Record Guide). The screening may be conducted by a case manager, a therapist, or other children's mental health professional.
- **XVI.D.5.** Results of the FASD screening and FASD diagnostic evaluations, if indicated, must be reflected in the child's Individual Service Plan and/or

Case Management Service 185 Plan. If a child receives a fetal alcohol-related diagnosis, it should be recorded on the appropriate Axis.

- **XVI.D.6.** If a child's initial FASD screening result is negative and if additional information regarding maternal alcohol history is obtained that might change the results of the initial FASD screen from negative to positive for possible prenatal alcohol exposure, the result of the initial screening must be revised on the FASD Screening Form to reflect this change and a diagnostic evaluation must be sought.
- **XVI.D.7.** With consent obtained from the parent/legal guardian, children who receive a positive FASD screen should be referred to the Child Development Clinic at the University of Mississippi Medical Center or other multi-disciplinary children's clinic qualified to diagnose FASD for a diagnostic evaluation. With consent obtained from the parent/legal guardian, best practice requires a provider staff person to accompany the child and parent/guardian to the diagnostic appointment in order to participate in the child's history interview and the informational interview. If this best practice is not followed, the child's record must be documented to show the effort put forth by the staff person to attend the diagnostic appointment and the reason this did not occur. A copy of the full diagnostic report must be placed in the child's record.
- **XVI.D.8.** Treatments and interventions recommended by the FASD multi-disciplinary diagnostic team must be either provided or facilitated by the CMHC. Referral to the local MAP Team should be made when appropriate.
- **XVI.D.9.** Because children with an FASD often are not able to respond to traditional mental health services and/or treatments, children's mental health services may need to be modified in order to be more effective for children with an FASD. FASD services and service modifications must be documented in the child's record.

[1] The FASD screening tool referred to in operational standard **XVI.D.3** is available on pp. 129-131 of the *Department of Mental Health Record Guide for Mental Health, Intellectual and Developmental Disabilities, and Substance Abuse Community Providers, 2012 Revision* (**http://www.dmh.state.ms.us/pdf/DMH%20Record%20Guide%202012%20Revision.pdf**), published by the Mississippi Department of Mental Health. The tool is less extensive than the *FASD 4-Digit Code Caregiver Interview Checklist* included in Part 1, Chapter 2 of this TIP, and is intended primarily for use with children (although it is suggested for limited use with individuals ages 18-24).

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TIP 1 **State Methadone Treatment Guidelines**—*Replaced by TIP 43*

TIP 2* **Pregnant, Substance-Using Women**—BKD107

TIP 3 **Screening and Assessment of Alcohol- and Other Drug-Abusing Adolescents**—*Replaced by TIP 31*

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TIP 12 **Combining Substance Abuse Treatment With Intermediate Sanctions for Adults in the Criminal Justice System**—*Replaced by TIP 44*

TIP 13 **Role and Current Status of Patient Placement Criteria in the Treatment of Substance Use Disorders**—BKD161
Quick Guide for Clinicians QGCT13
Quick Guide for Administrators QGAT13
KAP Keys for Clinicians KAPT13

*Under revision

TIP 14 **Developing State Outcomes Monitoring Systems for Alcohol and Other Drug Abuse Treatment**—BKD162

TIP 15 **Treatment for HIV-Infected Alcohol and Other Drug Abusers**—*Replaced by TIP 37*

TIP 16 **Alcohol and Other Drug Screening of Hospitalized Trauma Patients**—BKD164
Quick Guide for Clinicians QGCT16
KAP Keys for Clinicians KAPT16

TIP 17 **Planning for Alcohol and Other Drug Abuse Treatment for Adults in the Criminal Justice System**—*Replaced by TIP 44*

TIP 18 **The Tuberculosis Epidemic: Legal and Ethical Issues for Alcohol and Other Drug Abuse Treatment Providers**—BKD173
Quick Guide for Clinicians QGCT18
KAP Keys for Clinicians KAPT18

TIP 19 **Detoxification From Alcohol and Other Drugs**—*Replaced by TIP 45*

TIP 20 **Matching Treatment to Patient Needs in Opioid Substitution Therapy**—*Replaced by TIP 43*

TIP 21 **Combining Alcohol and Other Drug Abuse Treatment With Diversion for Juveniles in the Justice System**—(SMA) 08-4073
Quick Guide for Clinicians and Administrators QGCA21

TIP 22 **LAAM in the Treatment of Opiate Addiction**—*Replaced by TIP 43*

TIP 23 **Treatment Drug Courts: Integrating Substance Abuse Treatment With Legal Case Processing**—(SMA) 08-3917
Quick Guide for Administrators QGAT23

TIP 24 **A Guide to Substance Abuse Services for Primary Care Clinicians**—(SMA) 08-4075
Concise Desk Reference Guide BKD123
Quick Guide for Clinicians QGCT24
KAP Keys for Clinicians KAPT24

TIP 25 **Substance Abuse Treatment and Domestic Violence**—(SMA) 08-4076
Linking Substance Abuse Treatment and Domestic Violence Services: A Guide for Treatment Providers MS668
Linking Substance Abuse Treatment and Domestic Violence Services: A Guide for Administrators MS667
Quick Guide for Clinicians QGCT25
KAP Keys for Clinicians KAPT25

TIP 26 **Substance Abuse Among Older Adults**—(SMA) 08-3918
Substance Abuse Among Older Adults: A Guide for Treatment Providers MS669
Substance Abuse Among Older Adults: A Guide for Social Service Providers MS670
Substance Abuse Among Older Adults: Physician's Guide MS671
Quick Guide for Clinicians QGCT26
KAP Keys for Clinicians KAPT26

TIP 27 **Comprehensive Case Management for Substance Abuse Treatment**—(SMA) 08-4215
Case Management for Substance Abuse Treatment: A Guide for Treatment Providers MS673
Case Management for Substance Abuse Treatment: A Guide for Administrators MS672
Quick Guide for Clinicians QGCT27
Quick Guide for Administrators QGAT27

TIP 28* **Naltrexone and Alcoholism Treatment**—Replaced by TIP 49

TIP 29 **Substance Use Disorder Treatment for People With Physical and Cognitive Disabilities**—(SMA) 08-4078
Quick Guide for Clinicians QGCT29
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KAP Keys for Clinicians KAPT29

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Quick Guide for Clinicians QGCT30
KAP Keys for Clinicians KAPT30

TIP 31 **Screening and Assessing Adolescents for Substance Use Disorders**—(SMA) 08-4079
See companion products for TIP 32.

TIP 32 **Treatment of Adolescents With Substance Use Disorders**—(SMA) 08-4080
Quick Guide for Clinicians QGC312
KAP Keys for Clinicians KAP312

TIP 33 **Treatment for Stimulant Use Disorders**—(SMA) 06-4209
Quick Guide for Clinicians QGCT33
KAP Keys for Clinicians KAPT33

*Under revision

TIP 34 **Brief Interventions and Brief Therapies for Substance Abuse**—(SMA) 07-3952
Quick Guide for Clinicians QGCT34
KAP Keys for Clinicians KAPT34

TIP 35 **Enhancing Motivation for Change in Substance Abuse Treatment**—(SMA) 08-4212
Quick Guide for Clinicians QGCT35
KAP Keys for Clinicians KAPT35

TIP 36 **Substance Abuse Treatment for Persons With Child Abuse and Neglect Issues**—(SMA) 08-3923
Quick Guide for Clinicians QGCT36
KAP Keys for Clinicians KAPT36
Helping Yourself Heal: A Recovering Woman's Guide to Coping With Childhood Abuse Issues—(SMA) 08-4132
Available in Spanish: PHD981S
Helping Yourself Heal: A Recovering Man's Guide to Coping With the Effects of Childhood Abuse—(SMA) 08-4134
Available in Spanish: PHD1059S

TIP 37 **Substance Abuse Treatment for Persons With HIV/AIDS**—(SMA) 08-4137
Quick Guide for Clinicians MS678
KAP Keys for Clinicians KAPT37
Drugs, Alcohol, and HIV/AIDS: A Consumer Guide—(SMA) 08-4127
Drugs, Alcohol, and HIV/AIDS: A Consumer Guide for African Americans—(SMA) 07-4248

TIP 38 **Integrating Substance Abuse Treatment and Vocational Services**—(SMA) 06-4216
Quick Guide for Clinicians QGCT38
Quick Guide for Administrators QGAT38
KAP Keys for Clinicians KAPT38

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Quick Guide for Administrators QGAT39

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TIP 41 **Substance Abuse Treatment: Group Therapy**—(SMA) 05-3991
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Quick Guide for Clinicians (SMA) 07-4034
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KAP Keys for Clinicians (SMA) 08-4036

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Quick Guide for Counselors (SMA) 10-4542
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*Under revision

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TIP 53 Addressing Viral Hepatitis in People With Substance Use Disorders—(SMA) 11-4656

TIP 54 Managing Chronic Pain in Adults With or in Recovery From Substance Use Disorders—(SMA) 11-4661

TIP 55 Behavioral Health Services for People Who Are Homeless—(SMA) 13-4734

TIP 56 Addressing the Specific Behavioral Health Needs of Men—(SMA) 13-4736

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TWENTY YEARS OF PATIENT SURVEYS CONFIRM A FASD 4-DIGIT-CODE INTERDISCIPLINARY DIAGNOSIS AFFORDED SUBSTANTIAL ACCESS TO INTERVENTIONS THAT MET PATIENTS' NEEDS

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ABSTRACT

Background
2013 marks the 40th year since the term fetal alcohol syndrome (FAS) was coined at the University of Washington. In 1993, the University of Washington opened the first interdisciplinary FASD diagnostic clinic; expanded to a statewide network of clinics in 1995 (Washington State FAS Diagnostic & Prevention Network (WA FASDPN)), and introduced a new, rigorous diagnostic system, the fetal alcohol spectrum disorder (FASD) 4-Digit Diagnostic Code in 1997. The WA FASDPN mission is FASD primary and secondary prevention. Evidence of successful primary prevention (fewer alcohol-exposed pregnancies and FAS births) was documented in WA in the 1990s. Secondary prevention (reduction of disability among individuals with prenatal alcohol exposure) starts with accurate diagnoses and access to interventions that meet patients' needs.

Objective
Do patients report an FASD diagnostic evaluation affords them access to interventions that meet their needs?

Methods
Twenty years of follow-up surveys from 622 patients (birth through adult) who received an interdisciplinary FASD diagnostic evaluation at the University of Washington FASDPN using the 4-Digit Code were reviewed.

Results
Patients (99%) expressed high satisfaction in the FASD diagnostic process and outcome. Patients reported success accessing (89%) recommended interventions that met their needs (>96%). Patients with Neurobehavioral-Disorder/Alcohol-Exposed and Static-Encephalopathy/Alcohol-Exposed were as successful accessing interventions that met their needs as patients with FAS/Partial-FAS. Families of patients 0-5 years old reported the greatest access and needs met.

Conclusions
Patient surveys confirm an interdisciplinary diagnosis using the 4-Digit Code affords them substantial access to interventions that meet their needs across the spectrum of FASD diagnoses.

Key Words: *Fetal alcohol spectrum disorder (FASD), Fetal alcohol syndrome (FAS), FASD 4-Digit Diagnostic Code, Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network (WA FASDPN) Intervention*

What is FASD?
Fetal Alcohol Syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. The condition is characterized by prenatal and/or postnatal growth deficiency, a unique cluster of minor facial anomalies, and central nervous system (CNS) abnormalities.[1-3] FAS is the leading known preventable cause of intellectual disabilities in the

Western World.[4] The prevalence of FAS is estimated to be 1 to 3 per 1,000 live births[5] in the general population, 10 to 15 per 1,000 in some higher-risk populations such as children residing in foster care[6,7], and 100 per 1,000 in our statewide fetal alcohol spectrum disorder (FASD) diagnostic clinics (the WA FAS Diagnostic & Prevention Network (WA FASDPN)).[8] Not all individuals damaged by prenatal alcohol exposure have FAS; the majority present with moderate to severe CNS abnormalities without the physical features. This full spectrum of adverse outcomes caused by prenatal alcohol exposure is referred to as Fetal Alcohol Spectrum Disorders (FASD). Diagnoses like FAS, Partial FAS (PFAS), Static Encephalopathy/Alcohol Exposed (SE/AE), and Neurobehavioral Disorder/Alcohol Exposed (ND/AE) fall under the umbrella of FASD.[3] The prevalence of SE/AE and ND/AE is 6-fold greater than the prevalence of FAS/PFAS in the population of individuals receiving FASD diagnostic evaluations at our statewide FASD diagnostic clinics (WA FASDPN) over the past 20 years.

The Role of an FASD Diagnostic Clinic in Primary and Secondary FASD Prevention

The year 2013 marks the 40th year since the term FAS was first coined at the University of Washington.[9] The year 2013 also marks the 20th year of the WA FASDPN diagnostic clinics.[8,10] The mission of the WA FASDPN is primary and secondary prevention of FASD through screening, diagnosis, surveillance, intervention, research, and education. In 1992, we postulated that an FASD diagnostic clinic could and should play a central role in FASD prevention; both primary prevention (reduction in prevalence of alcohol consumption during pregnancy and FASD) and secondary prevention (mitigation of disabilities among individuals with FASD). Empirical evidence now exists confirming and illustrating the central role of an FASD clinic in primary prevention of FASD.[6,11,12,7,13] The focus of the current study is the role of a FASD diagnostic clinic in secondary prevention of FASD. Secondary prevention is a level of health care that focuses on early diagnosis, use of referral services, and rapid initiation of treatment to stop the progress of disease processes or a handicapping disability.[14] In this report, the disease process or handicapping disability is FASD. As stated in the 1996 Institute of Medicine Report[5] on FASD "Children with FAS or ARND have impairments that cannot be normalized, but possibly can be improved with appropriate interventions, and they can possibly be made worse when ignored or misunderstood."

Over the past 20 years interdisciplinary FASD diagnostic clinics have opened worldwide.[2] The FASDPN has trained over 100 interdisciplinary teams in over 16 countries.[15,16] An important public health question that remains largely unanswered is "What is the direct benefit of a FASD diagnostic evaluation?" Does an FASD diagnostic evaluation lead to improved patient outcome? An important component of the FASD diagnostic process is to provide patients with a comprehensive set of intervention recommendations specific to their needs.[17-20] These recommendations are collectively generated by the interdisciplinary diagnostic team at the UW FAS DPN.[17] These recommendations include resources, referrals, and strategies that address presenting clinical concerns in areas such as health, behavior, social welfare, and education. The WA FAS DPN diagnostic teams share these intervention recommendations with caregivers at the end of the 4-hour FASD diagnostic evaluation. These recommendations are included in the patient's FASD Medical Summary Report which is submitted to their medical record. A comprehensive summary of the types and frequencies of recommendations provided to patients across all ages and FASD diagnostic classifications is presented by Jirikowic et al.[17]

Study Objectives

Over the past 20 years 2,550 patients have received an FASD diagnostic evaluation at the WA FASDPN by an interdisciplinary team using the FASD 4-Digit Diagnostic Code.[2,8] At the conclusion of their 4-hour evaluation, 78% received a diagnosis broadly under the umbrella of FASD (FAS (4%), PFAS (6%), SE/AE (24%) or ND/AE (44%)) and all received a comprehensive set of intervention recommendations. All families who attend the University of Washington FASDPN clinic receive a Patient Follow-Up Survey (Figure 1) several months after their diagnostic evaluation.

The objective of this study was to evaluate these patient surveys to answer the following questions:

1. Do families report a high level of satisfaction and confidence in the interdisciplinary FASD diagnostic process and outcome?
2. Do families report obtaining information from the FASDPN clinic they were unable to obtain elsewhere?
3. Did they find the 4-Digit Code method of diagnosis easy to understand?
4. Were families able to find/access the intervention services recommended by the clinic?
5. If they were able to access the interventions, did the interventions meet their needs?
6. Were the responses to the above questions influenced by the patient's age, diagnostic classification, or method of diagnosis (gestalt versus 4-Digit Code)?

METHODS

Interdisciplinary FASD Diagnostic Model

When the University of Washington FASD diagnostic clinic first opened in January 1993, it was the first to propose/implement an interdisciplinary approach to diagnosis[21,22] through a CDC-sponsored FAS prevention project conducted in 1992- 97.[11,12] In 1995, State legislative action (Senate Bill 5688) expanded the single clinic to a statewide network of FASD diagnostic clinics; the WA FASDPN, led by the core clinic at the University of Washington (UW). Because of the complexity and broad array of outcomes observed in individuals with prenatal alcohol exposure, an interdisciplinary team was deemed essential for an accurate and comprehensive diagnosis and intervention plan. Our interdisciplinary FASD diagnostic teams include a medical doctor, psychologist, speech language pathologist, occupational therapist, social worker, and family advocate.[2]

The patient population served by the WA FASDPN has always expressed strong preference for an evaluation that can be completed in one visit. Thus, our FASD diagnostic evaluation is conducted in one 4-hour session. In preparation for the evaluation, the patient's birth, medical, school, psychological, and social service records are collected by the clinic coordinator and pre-reviewed by the lead psychologist or social worker. On the day of the evaluation, the lead psychologist or social worker presents the patient's case history, including the outcomes of any prior medical/psychological assessments, to the team in a 30-minute case conference. While the case-conference is being conducted, the patient's growth is measured and facial photograph is taken for computerized analysis.[23] After the case-conference, the pediatrician and lead psychologist or social worker conduct an interview with the caregiver(s) while the child is assessed over a 2-hour period by the second psychologist, speech-language pathologist, and occupational therapist. The child receives a brief physical examination by the pediatrician at the end of their 2-hour assessment. The caregiver interview and child assessment sessions focus on gathering information that is needed to render an accurate diagnosis and are not already present in the child's records. The battery of assessments administered to each patient (both historically and on the day of the diagnostic evaluation) vary by patient age and area(s) of developmental concern. The team reconvenes for 1 hour to derive the FASD 4-Digit Code and generate an intervention plan. The diagnosis and intervention plan are shared with the family in the final 30 minutes of the evaluation. A single, comprehensive FASD Medical Summary Report documenting the diagnostic outcome, all data used to derive the diagnostic outcome, and intervention recommendations are submitted to the patient's medical record.

Intervention Recommendations

An important component of our FASD diagnostic process is to provide patients with a comprehensive set of intervention recommendations specific to their needs.[17,18,20] These intervention recommendations are collectively generated by the interdisciplinary diagnostic team at the completion of the 4-hour FASD diagnostic evaluation. These recommendations include resources, referrals, and strategies that address presenting clinical concerns

in areas such as health, behavior, social welfare, and education. The UW FASDPN has compiled over 200 intervention recommendations in a Microsoft Word template (each assigned a unique key code) that allows for rapid construction of individualized intervention plans by the interdisciplinary team during the course of the 4-hour diagnostic evaluation. These intervention recommendations are shared with caregivers at the end of the 4-hour diagnostic evaluation and are included in the patient's FASD Medical Summary Report that is submitted to their medical record.

A recent study published by members of the UW FASDPN diagnostic team[17] summarized the type and frequency of intervention recommendations provided to patients receiving diagnoses under the spectrum of FASD at the UW FASDPN diagnostic clinic. The focus of the study was to assess how recommendations varied by FASD diagnostic groups and selected sociodemographic characteristics (e.g., age, gender, and caregiver status). In preparation for the study, a coding system was developed to categorize the 200+ intervention recommendations into 12 sub-categories as presented in Table 1 and described more fully by Jirkowic et al.[17] Findings reported by Jirikowic et al[17] indicated that children with FASD, like children with other neurodevelopmental disabilities, have a wide range of complex and specialized needs that span across systems of care. Although FAS has historically been considered among the most severe outcomes of prenatal alcohol exposure, these data show that similar intervention recommendations and needs were seen for children across the full spectrum of diagnoses under the umbrella of FASD.

Starting in 2007, all patients evaluated in the UW FASDPN clinic have had their intervention recommendations coded in accordance with the system described above and entered into the FASDPN clinical/research database described below.

TABLE 1 Intervention recommendation categories and examples[17] (Figure 4)

Category	Examples
Family Support–Resources: Referral/ recommendations for educational materials (e.g., books, Web sites) community support groups, advocacy training, or caregiver education or support.	1. Books, Web-based resources (e.g., attachment, sleep, FASD). 2. Personal/peer support (e.g., National Organization or Fetal Alcohol Syndrome [NOFAS], grandparent support group). 3. Advocacy/education (e.g., parent advocacy group, parent education, community training). 4. Respite/self-care for caregiver.
Medical: Recommendation/referral to medical specialist or current provider for evaluation or follow-up care regarding a specific medical problem or issue.	1. Psychiatric services and/or medication management/consultation. 2. ADHD evaluation 3. Sleep evaluation 4. Vision/hearing evaluation 5. Growth 6. Neurological evaluation/consultation 7. Genetic work up or consultation
Anticipatory Guidance / Prevention: Prevention oriented recommendations based on developmental risk factors for future problems.	1. Substance abuse prevention 2. Learning problems/behavior risks (awareness of potential for school/learning difficulties and/or mental health problems). 3. Reproductive health (e.g., pregnancy and STD prevention).
Social service / Child Welfare: Resources/support for children in out of home placements, including caregiver support and funding resources.	1. Placement advocacy (e.g., stable, safe, structured, supportive home environment; movement towards long-term permanency). 2. Caregiver resources to support appropriate placements and long-term needs (e.g., adoption support, supplemental security income eligibility, family support program).

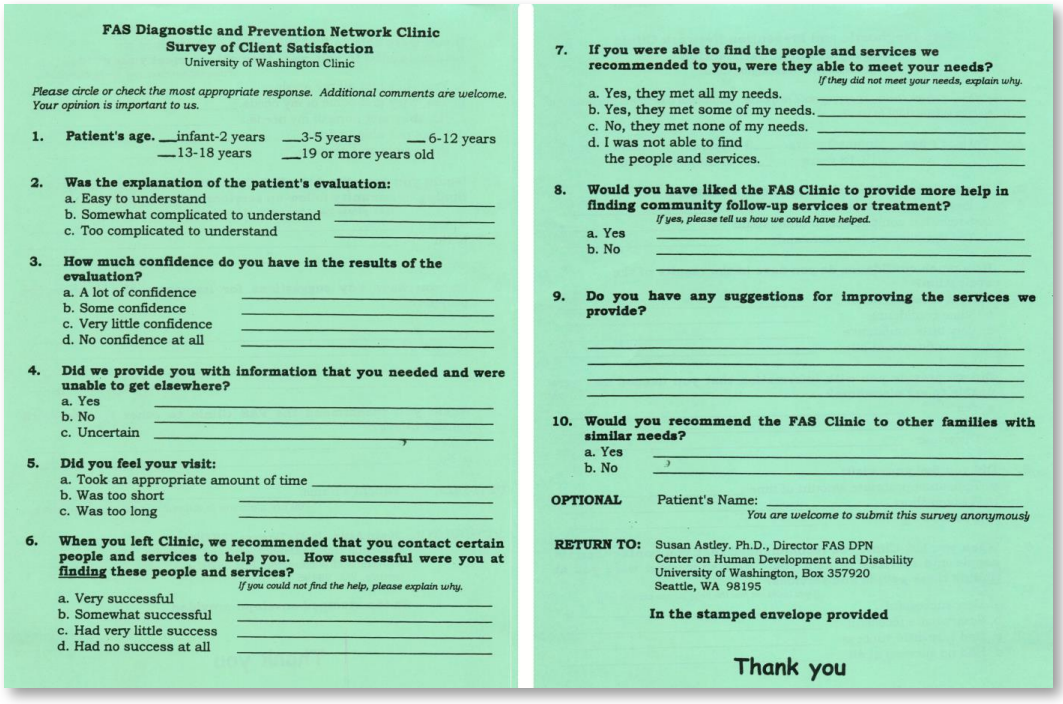
The value of a FASD diagnosis (2013)

Developmental Therapy: Referral/recommendation for occupational therapy, physical therapy, speech-language therapy, or specific therapeutic program.	1. Referral to OT 2. Referral to SLP 3. Referral to a social skills group. 4. Referral to another therapeutic program.
Education/Assessment: Referral, advocacy, or support for a specific educational program or service, psycho-educational assessment, or specific skill area that requires educational monitoring.	1. Referral/support for educational service (e.g., special education, life skills training, birth to 3 year program). 2. Monitor a specific area of performance (e.g., fine motor, language). 3. Psychoeducational–neuropsychological assessment to determine special education eligibility, re-examine individual education plan or advocate for continued eligibility.
Community-based Activities: Leisure or recreation recommendations for specific, community-based activities/programs that are prosocial, recreational, extracurricular in nature and include appropriate developmental and social supports.	1. Prosocial extracurricular/play activities (e.g., Boys and Girls Club; community social skills groups). 2. Physical/movement (e.g., noncompetitive sports; therapeutic horseback riding; Special Olympics). 3. Special interest groups (e.g., focused leisure, religious, or cultural activities). 4. Adult mentor (e.g., Big Brother/Big Sister).
Safety Awareness: Recommendations/resources to address home, school, or community safety concerns.	1. Personal ID/safety (e.g., ID bracelet, wallet card). 2. Environmental modification/supervision (e.g., alarms, line-of-sight supervision).
Mental health: Support/referral for mental health services to address individual and/or family needs around behavior, development, or mental health problem.	1. Behavioral consultation or specialist (e.g., behavior management, home-based intervention services). 2. Individual counseling 3. Family counseling 4. Case management
Adult Transition / Future Planning:	1. Vocational 2. Financial 3. Other future plan.
Accommodations: Specific adaptation or modification to environment/routine to be implemented in home, school, or other setting.	1. Behavior/emotional regulation (e.g., supports for group participation, enhancing environmental structure). 2. Communication (e.g., visual schedules, cues for social interaction). 3. Executive function, organization, memory (e.g., memory aids, checklists). 4. Sensory–motor (e.g., headphones, reducing sensory input, keyboarding). 5. Team communication (e.g., communication between home, school, and other providers).
Developmental Therapy: Referral/recommendation for occupational therapy, physical therapy, speech–language therapy, or specific therapeutic program.	1. Referral/recommendation for occupational, physical, or speech language therapy evaluation or treatment. 2. Referral to a therapeutic social skills group.
Other	1. Substance abuse recommendations supporting treatment or recovery (caregiver or patient). 2. FASD re-evaluation

Patient Follow-Up Survey

A 10-question patient follow-up survey (Figure 1) has been sent to all patients evaluated at the University of Washington FASDPN clinic since 1993. The survey is mailed approximately 3 months after the patient's FASD diagnostic evaluation and comes with a stamped, addressed return envelope to maximize participation. The family may elect to submit the survey anonymously, or they can choose to enter the patient's name on the survey. The survey queries the patient's satisfaction with the diagnostic

process; their confidence in the outcome; how successful they were at finding and accessing the interventions the diagnostic team recommended; and to what extent the interventions met their needs.



FAS Diagnostic and Prevention Network Clinic
Survey of Client Satisfaction
University of Washington Clinic

Please circle or check the most appropriate response. Additional comments are welcome. Your opinion is important to us.

1. **Patient's age.** __infant-2 years __3-5 years __6-12 years __13-18 years __19 or more years old
2. **Was the explanation of the patient's evaluation:**
   a. Easy to understand
   b. Somewhat complicated to understand
   c. Too complicated to understand
3. **How much confidence do you have in the results of the evaluation?**
   a. A lot of confidence
   b. Some confidence
   c. Very little confidence
   d. No confidence at all
4. **Did we provide you with information that you needed and were unable to get elsewhere?**
   a. Yes
   b. No
   c. Uncertain
5. **Did you feel your visit:**
   a. Took an appropriate amount of time
   b. Was too short
   c. Was too long
6. **When you left Clinic, we recommended that you contact certain people and services to help you. How successful were you at finding these people and services?**
   If you could not find the help, please explain why.
   a. Very successful
   b. Somewhat successful
   c. Had very little success
   d. Had no success at all
7. **If you were able to find the people and services we recommended to you, were they able to meet your needs?**
   If they did not meet your needs, explain why.
   a. Yes, they met all my needs.
   b. Yes, they met some of my needs.
   c. No, they met none of my needs.
   d. I was not able to find the people and services.
8. **Would you have liked the FAS Clinic to provide more help in finding community follow-up services or treatment?**
   If yes, please tell us how we could have helped.
   a. Yes
   b. No
9. **Do you have any suggestions for improving the services we provide?**
10. **Would you recommend the FAS Clinic to other families with similar needs?**
    a. Yes
    b. No

OPTIONAL Patient's Name:
You are welcome to submit this survey anonymously

RETURN TO: Susan Astley. Ph.D., Director FAS DPN
Center on Human Development and Disability
University of Washington, Box 357920
Seattle, WA 98195

In the stamped envelope provided

Thank you

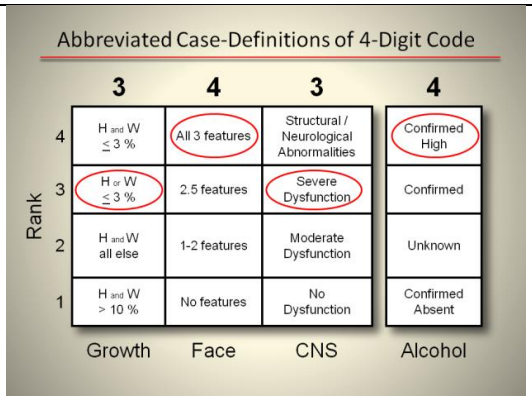
FIG. 1 Patient Follow-up Survey mailed to all patients approximately three months after their FASD diagnostic evaluation at the University of Washington FAS Diagnostic & Prevention Network clinic.

FASD Diagnostic Systems Used

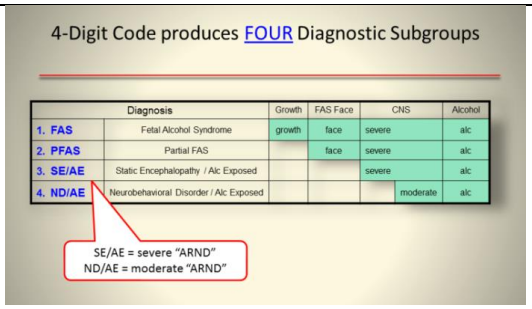
When the University of Washington FASD diagnostic clinic first opened in January 1993, the interdisciplinary team used the most current FASD diagnostic guidelines available at that time; the 1989 gestalt diagnostic criteria published by Sokol and Clarren.[24] In 1996, the Institute of Medicine (IOM) published an updated set of FASD diagnostic guidelines[5], but continued to propose a gestalt approach. The gestalt approach to diagnosis presented with many limitations.[2,10,25] The UW FASDPN created the 4-Digit Code in 1997 to overcome these limitations.[26] Thus, from 1993 through 1996, patients experienced an interdisciplinary team using a gestalt[24] approach to diagnosis. Only two FASD diagnostic classifications were rendered back then; FAS and Probable fetal alcohol effects (PFAE). PFAE was equivalent to what the IOM now calls ARND.[5] In 1997, the WA FASDPN interdisciplinary teams started using the FASD 4-Digit Diagnostic Code.[3,25] Diagnostic classifications include FAS, PFAS, SE/AE and ND/AE, as explained more fully below.

In 1997 the FASDPN switched from the gestalt[24] method of diagnosis to the FASD 4-Digit Diagnostic Code.[3,25,26] Briefly, the 4 digits of the FASD 4-Digit Code reflect the magnitude of

expression of the 4 key diagnostic features of FASD, in the following order: 1. Growth deficiency, 2. FAS facial phenotype, 3. CNS structural/functional abnormalities, and 4. Prenatal alcohol exposure (Figure 2A). The magnitude of expression of each feature is ranked independently on a 4-point Likert scale, with 1 reflecting complete absence of the FASD feature and 4 reflecting a strong "classic" presence of the FASD feature. Each Likert rank is specifically case defined. There are a total of 102 4-Digit Codes that fall broadly under the umbrella of FASD (Table 2). These codes cluster under four clinically meaningful FASD diagnostic subcategories: fetal alcohol syndrome (FAS): Diagnostic Categories A and B; Partial FAS (PFAS): Diagnostic Category C; Static Encephalopathy/Alcohol-Exposed (SE/AE): Diagnostic Categories E and F; and Neurobehavioral Disorder/Alcohol-Exposed (ND/AE): Diagnostic Categories G and H (Figure 2B). The attributes of the 4-Digit Code are summarized in Astley.[10]



A



B

FIG. 2 A. Abbreviated case-definitions of the FASD 4-Digit Code.[3] The 4-Digit Code 3434 is one of 12 Codes that fall under the diagnostic category FAS/Alcohol-Exposed (Table 2). **B**. The FASD 4-Digit Code diagnostic system produces four diagnostic subgroups under the umbrella of FASD: FAS, PFAS, SE/AE, and ND/AE.[2,8,10] The 4-Digit Code does not use the term Alcohol Related Neurodevelopmental Disorder (ARND). The terms SE/AE and ND/AE are used in place of the term ARND.

TABLE 2 4-Digit Diagnostic Codes within each FASD Diagnostic Category (2004)[3]

A. FAS / Alcohol Exposed

2433	3433	4433
2434	3434	4434
2443	3443	4443
2444	3444	4444

B. FAS / Alcohol Exposure Unknown

2432	3432	4432
2442	3442	4442

C. Partial FAS /Alcohol Exposed

1333	1433	2333	3333
1334	1434	2334	3334
1343	1443	2343	3343
1344	1444	2344	3344

E. Sentinel Physical Finding(s) / Static Encephalopathy / Alcohol Exposed

3133	3233	4133	4233
3134	3234	4134	4234
3143	3243	4143	4243
3144	3244	4144	4244

F. Static Encephalopathy / Alcohol Exposed

1133	1233	2133	2233
1134	1234	2134	2234
1143	1243	2143	2243
1144	1244	2144	2244

G. Sentinel Physical Finding(s) / Neurobehavioral Disorder / Alcohol Exposed

1323	2323	3123	3323	4123	4323
1324	2324	3124	3324	4124	4324
1423	2423	3223	3423	4223	4423
1424	2424	3224	3424	4224	4424

H. Neurobehavioral Disorder / Alcohol Exposed

1123	1223	2123	2223
1124	1224	2124	2224

WA FASDPN Clinical/Research Database

All data collected by the WA FASDPN clinics since 1993 has been entered into an electronic clinical/research database with patient consent and Human Subjects Review Board approval.[2,10] To date, there are over 2,000 fields of information entered on over 7,000 patients requesting an evaluation and 2,550 patients who have received an evaluation to date. The majority of the data entered into the database comes from the following standardized data forms: 1) the New Patient Information Form; 2) the FASD Diagnostic Form; 3) the FAS Facial Photographic Analysis Software Report; 4) the Medical Summary that includes the Intervention Recommendations; and 5) the Patient Follow-Up

Surveys. These forms are provided in the Diagnostic Guide for FASD[3] and/or are posted on the WA FASDPN website **(www.fasdpn.org)**.

Clinical Population and Study Groups

The clinical population from which the study population was drawn is all patients (n = 2, 550) who received an interdisciplinary FASD diagnostic evaluation throughout the 20 year history of the WA FASDPN. The WA FASDPN consists of a core clinic at the University of Washington and 7 Network FASD diagnostic clinics statewide.

Of the 2,550 patients evaluated at the WA FASDPN from 1993 through 2012, 1,545 (61%) were evaluated at the University of Washington clinic. All 1,545 patients evaluated at the University of Washington clinic received patient follow-up surveys 3 months after their FASD diagnostic evaluation. Of the 1,545 patients who received surveys, 622 (40%) completed and returned the surveys. These 622 patients are the focus of this study and were divided into the following study groups to facilitate the analysis/interpretation of their survey outcomes:

The 622 patients who returned patient follow-up surveys were divided into two groups (A & B) based on the FASD diagnostic method used for their evaluation.

A. Gestalt Diagnostic Method (N = 227):

All patients evaluated from 1993 through 1996 were evaluated by the UW interdisciplinary team using a gestalt[24] method of FASD diagnosis.

Twenty-one percent of this group received a gestalt diagnosis of FAS and 60% received a diagnosis of PFAE. Group A was not further divided into the gestalt diagnostic subgroups (like Group B below) because a previous study[25,27] confirmed this gestalt approach to diagnosis led to highly variable and inaccurate diagnostic classifications. Astley[25] confirmed that 75% of the gestalt FAS diagnoses were ruled out when the individual's outcomes are retrofitted to the more rigorous criteria of the 4-Digit Code.

B. FASD 4-Digit Diagnostic Code (N = 395):

All patients evaluated from 1997 through 2012 were evaluated by an interdisciplinary team using the FASD 4-Digit Diagnostic Code.[3,25]

All patients in Group B were further subdivided into six groups based on their 4-Digit Code diagnostic outcomes. Groups B1-4 fall broadly under the umbrella of FASD. The diagnostic features specific to each group were as follows:

1. *Patients in Group B1* had a 4-Digit diagnosis of **FAS or Partial FAS (FAS/PFAS)** (e.g., 4- Digit Diagnostic Categories A,B,C: with Growth Ranks 1-4, Face Ranks 3-4, CNS Ranks 3 and/or 4, Alcohol Ranks 2-4)[3] (Figure 2). Alcohol Rank 2 (unknown exposure) could only be present if the patient had a diagnosis of full FAS because the Rank 4 FAS facial features are so specific to prenatal alcohol exposure.[6,10,28-32] In summary, patients in Group 1 had severe CNS structural and/or functional abnormalities and the full FAS facial phenotype.

2. *Patients in Group B2* had a 4-Digit diagnosis of **Static Encephalopathy / Alcohol-Exposed (SE/AE)** (e.g., 4-Digit Diagnostic Categories E,F: with Growth Ranks 1-4, Face Ranks 1-2, CNS Ranks 3 and/or 4, Alcohol Ranks 3-4).[3] In summary, patients in Group 2 had severe cognitive/behavioral dysfunction, comparable to Group 1, but did not have the FAS facial phenotype.

3. *Patients in Group B3* had a 4-Digit diagnosis of **Neurobehavioral Disorder / Alcohol-Exposed (ND/AE)** (e.g. 4-Digit Diagnostic Categories G, H: with Growth Ranks 1-4, Face Ranks 1-2, CNS Rank 2, Alcohol Ranks 3-4).[3] In summary, patients in Group 3 had prenatal alcohol exposure comparable to Groups 1 and 2, but in comparison to Groups 1 and 2 had moderate cognitive/behavioral dysfunction, and did not have the FAS facial phenotype.

4. *Patients in Group B4* had a 4-Digit diagnosis of Sentinel Physical Findings/Alcohol-Exposed or No Physical Findings or CNS Abnormalities Detected / Alcohol-Exposed **(Normal CNS/AE**) (e.g., 4-Digit Diagnostic

Categories I and J: with Growth Ranks 1-4, Face Ranks 1-4, CNS Rank 1, and Alcohol Ranks 3-4).[3] In summary, patients in Group 4 had prenatal alcohol exposure, no CNS abnormalities, and may or may not have had growth deficiency and/or FAS facial features.

5. *Patients in Group B5* do not qualify for a diagnosis under the umbrella of FASD because their prenatal alcohol exposure is unknown or confirmed absent (**Not FASD**) (e.g., 4-Digit Diagnostic Categories D, K-V).[3] In summary, patients in Group 5 may have growth, facial, and/or CNS outcomes that span the full continuum from normal to abnormal, but in the absence of prenatal alcohol exposure, their outcomes cannot be attributed to prenatal alcohol exposure. Although patients are required to have a confirmed prenatal alcohol exposure to obtain an evaluation in the UW FASDPN clinic, this subset of patients had their exposure status reclassified to unknown (Rank 2) at the time of diagnosis when further information about their exposure status became available.

6. *Patients in Group B6* submitted Patient Follow-up Surveys anonymously, thus their identity and **Diagnostic Classification** are **unknown**. Patients in this group may span the full continuum of diagnostic classifications described for Groups B1-5.

Data Analysis

This study is primarily descriptive in nature. Outcomes are summarized using means, standard deviations, and proportions (valid percentages). Chi-square statistics were used, when appropriate, to compare proportions between two or more groups. Two-tailed p-values were used with a significance level set a $p < 0.05$.

RESULTS

Clinical and Sociodemographic Profile of the WA FASDPN Patient Population

The clinical and sociodemographic profile of all 2,550 patients who received an interdisciplinary FASD diagnostic evaluation at one of the WA State WA FASDPN clinics from 1993 through 2012 is presented in Table 3. This clinical population spans the entire age range (birth to 6 yrs (33%); 6-18 yrs (62%), adults (5%)). The vast majority (76%) were in out-of-home placement at the time of their diagnostic evaluation.

Of the 2,550 WA State FASDPN patients, 1,545 (60.6%) were evaluated at the core University of Washington (UW) FASDPN clinic in Seattle, WA. These are the 1,545 patients who were mailed Follow-up Surveys over the past 20 years and are the focus of this study. This subset of 1,545 patients is highly representative of the entire WA FASDPN population. Their diagnostic profile and age distribution are near identical (within a percentage point) to the diagnostic profile and age distribution of patients evaluated across the entire WA FASDPN presented in Table 3.

The value of a FASD diagnosis (2013)

TABLE 3 Sociodemograhic profile of 2,550 patients evaluated for FASD over 20 Years (1993-2012) in the WA State FASDPN Clinics

	FASD Diagnostic Subgroups*																	
Characteristic	**1. 101 FAS/ 146 PFAS**			**2. SE/AE**			**3. ND/AE**			**4. Normal CNS/AE**			**5. Not FASD**			**Total**		
	N = 247 (10%)			**N = 604 (24%)**			**N = 1,117 (44%)**			**N = 197 (8%)**			**N = 385 (15%)**			**N = 2,550**		
Gender: N (valid%)																		
male	124		52.0	380		64.1	642		57.7	86		44.8	201		52.8	1433		56.1
Race: N (valid%)																		
White	132		55.2	277		46.7	541		48.5	83		42.9	217		57.3	1250		49.6
Black	30		12.3	34		5.8	86		7.7	17		8.6	12		3.1	178		7.1
Native Am/Can/Alaskan	8		3.4	67		11.4	98		8.8	12		6.1	21		5.6	207		8.2
All others (including mixed)	70		29.1	214		36.1	390		35.0	82		42.3	129		33.9	884		35.0
Age at diagnosis (yr): N (row-column valid%)																		
0 – 2.9	46	15.5	18.7	45	15.1	7.4	104	35.1	9.3	80	27.1	40.7	21	7.2	5.5	297	100	11.6
3 – 5.9	59	10.5	23.9	103	18.2	17.0	285	50.5	25.5	57	10.1	28.7	60	10.7	15.6	564	100	22.1
6 – 12.9	97	8.4	39.2	306	26.4	50.7	518	44.7	46.3	38	3.3	19.2	200	17.2	51.8	1158	100	45.4
13 – 18.9	25	6.0	10.0	119	29.0	19.8	174	42.2	15.6	17	4.0	8.4	77	18.7	19.9	411	100	16.1
19+	20	16.7	8.1	31	25.5	5.1	37	30.4	3.3	6	4.9	3.0	27	22.5	7.1	121	100	4.7
Mean (SD)	8.7		8.1	9.9		5.9	8.7		5.4	6.0		7.0	10.7		7.0	9.1		6.3
Minimum Maximum	0.3		50.5	0.5		50.8	0.5		37.0	0.2		48.1	0.6		46.2	0.2		50.8
Caregiver at diagnosis: N (valid%)																		
Birth mother	43		17.6	118		19.6	213		19.7	47		24.7	12		3.2	432		17.4
Other birth family member	57		23.4	116		19.2	249		23.1	48		25.9	69		18.6	540		21.7
Adoptive parent	60		24.9	164		27.3	275		25.4	27		14.2	152		41.2	679		27.3
Foster parent	63		25.9	135		36.8	271		25.0	56		29.1	115		31.0	638		25.6
Other	20		6.4	70		11.6	74		7.0	12		6.2	22		6.1	199		8.0

* 1) FAS/PFAS: fetal alcohol syndrome or partial FAS (4-Digit Diagnostic Categories A-C). 2) SE/AE: Static Encephalopathy/Alcohol-Exposed (4-Digit Diagnostic Categories E,F). 3) ND/AE: Neurodevelopmental Disorder/Alcohol-Exposed (4-Digit Diagnostic Categories G,H). 4) Normal CNS/AE; No Central Nervous System abnormalities/Alcohol-Exposed (4-Digit Diagnostic Categories I,J). 5) Not FASD-alcohol exposure unknown or absent (4-Digit Diagnostic Categories D,K-,V)[3].

Patient Follow-Up Surveys

Of the 1,545 Patient Follow-Up Surveys mailed out between 1993 and 2012 to patients evaluated at the UW FASDPN, 622 were completed and returned reflecting a 40% response rate. Although families were given the option to return the survey anonymously, 85% (n=527) chose to identify the name of the patient. This allowed us to connect their responses to the patient's diagnostic outcome. The 622 completed surveys are distributed equally across the 20 years (1993-2012) and reflect a patient population that is near identical to (highly representative of) the FASD diagnostic profile and age distribution of the larger patient populations from which they were pulled (the entire WA FASDPN population (n=2,550), and the subset of 1,545 from the UW FASDPN) (Tables 4 and 5). Of the 622 surveys, 277 (36%) were from patients receiving a gestalt diagnostic evaluation and 395 (64%) were from patients receiving a diagnostic evaluation using the 4-Digit Code.

Family Report of Satisfaction and Confidence

Families (n=395) reported high levels of satisfaction and confidence in the 4-Digit Code administered by the University of Washington interdisciplinary diagnostic team.[26] (Table 4).

Ninety-nine percent would recommend the Clinic to other families with similar needs. Ninety-two percent said they received information they were unable to obtain elsewhere. Eighty-three percent found the explanation of the diagnostic evaluation outcome easy to understand. Ninety-eight percent expressed confidence in the results of the evaluation. Ninety-one percent felt the single 4-hour evaluation was an appropriate length of time for the evaluation.

Measures of satisfaction and confidence were comparably high across all diagnostic sub-classifications (Tables 4, 5, Figure 3), but varied somewhat across age groups (Table 6, 7). The adult patients who returned surveys (18 individuals 19 years of age or older) were less likely to report the explanation of the diagnostic evaluation was easy to understand (53% of adults reported it was easy to understand versus 84% across all younger groups). When adults are evaluated in clinic, the results are shared back directly with the adult patient. In contrast, when children are evaluated, the results are shared with their caregiver(s). Since all 18 adult patients had moderate to severe CNS dysfunction, it is understandable why they might report it was somewhat more difficult to understand the results.

4-Digit Code Patient Follow-Up Surveys	FAS/PFAS %	SE/AE %	ND/AE %
Easy to understand	84	80	86
Confident in diagnosis	98	99	100
Provided information not received elsewhere	98	91	89
Successful at finding/accessing recommended services	90	93	90
Services met some to all of my needs	97	96	96
Would recommend clinic to other families with similar needs	100	100	100

FIG. 3 Patient follow-up surveys (n = 395) confirm families have a very high level of satisfaction and confidence in the 4-Digit Code administered by the University of Washington interdisciplinary diagnostic team. Family's whose child received a diagnosis of SE/AE or ND/AE were as likely to report successfully accessing recommended intervention services that met their needs as family's whose child received a diagnosis of FAS or FAS.

The value of a FASD diagnosis (2013)

TABLE 4 Summary of 395 Patient Follow-Up Surveys by 4-Digit Code FASD Diagnostic Classification: Satisfaction and Confidence in Diagnostic Evaluation

Questions	Diagnostic Subgroups*																				
	1. 14 FAS/ 29 PFAS			2. SE/AE			3. ND/AE			4. Normal CNS/AE			5. Not FASD			6. Diagnosis Unknown			Total		
	N = 43 (11%)			N = 92 (23%)			N = 132 (33%)			N = 27 (7%)			N = 39 (10%)			N=62 (16%)			N = 395		
	n	valid%		n	valid%		n	%		n	valid%		n	valid%		n	valid%		n	valid%	
		row	col		row	col		row	col		row	col		row	col		row	col		row	col
1. Patient's age at time of diagnosis																					
Birth to 2 years	11	16.9	25.6	8	12.3	8.7	19	29.2	14.5	13	20.0	48.	3	4.6	7.7	11	16.9	20.4	65	100	16.8
3-5 years	9	11.4	20.9	15	19.0	16.3	32	40.5	24.4	7	8.9	25.	6	7.6	15.	10	12.7	18.5	79	100	20.5
6-12 years	16	9.5	37.2	48	28.4	52.2	58	34.3	44.3	4	2.4	14.	20	11.8	51.	23	13.6	42.6	169	100	43.8
13-18 years	4	7.3	9.3	15	27.3	16.3	18	32.7	13.7	1	1.8	3.7	9	16.4	23.	8	14.5	14.8	55	100	14.2
19 or more years	3	16.7	7.0	6	33.3	6.5	4	22.2	3.1	2	11.1	7.4	1	5.6	2.6	2	11.1	3.7	18	100	4.7
Age (yrs)		Mean	SD		Mean	SD		Mean	SD		Mean	SD		Mean	SD		Mean	SD		Mean	SD
		8.6	10.3		10.2	6.1		8.4	5.7		6.8	9.1		9.9	5.8		--	--		8.9	6.9
2. Was the explanation of the evaluation:																					
Easy to understand	36		83.7	71		78.9	113		86.3	25		100.0	30		76.9	43		79.6	318		83.2
Somewhat complicated	7		16.3	19		21.1	18		13.7	0		.0	9		23.1	11		20.4	64		16.8
Too complicated to understand	0		0	0		0	0		0	0		0	0		0	0		0	0		0
3. How much confidence do you have in the evaluation results?																					
A lot of confidence	38		88.4	78		86.7	123		93.2	24		92.3	31		79.5	48		87.3	342		88.8
Some confidence	4		9.3	9		10.0	9		6.8	2		7.7	6		15.4	7		12.7	37		9.6
Very little confidence	1		2.3	3		3.3	0		.0	0		.0	2		5.1	0		.0	6		1.6
4. Did we provide information you needed and were unable to get elsewhere?																					
Yes	42		97.7	84		91.3	115		89.1	24		92.3	35		92.1	52		94.5	352		91.9
No	0		.0	5		5.4	5		3.9	1		3.8	2		5.3	1		1.8	14		3.7
Uncertain	1		2.3	3		3.3	9		7.0	1		3.8	1		2.6	2		3.6	17		4.4
5. Did you feel your visit:																					
Took an appropriate amount of time	38		88.4	80		87.9	118		92.9	22		91.7	38		97.4	47		88.7	343		91.0
Was too short	4		9.3	9		9.9	6		4.7	0		.0	1		2.6	5		9.4	25		6.6
Was too long	1		2.3	2		2.2	3		2.4	2		8.3	0		.0	1		1.9	9		2.4
9. Would you recommend the FAS Clinic to other families with similar needs?																					
Yes	43		100.0	88		100.0	132		100.0	26		100.0	38		97.4	51		98.1	378		99.5

* 1) FAS/PFAS: fetal alcohol syndrome or partial FAS (4-Digit Diagnostic Categories A-C). 2) SE/AE: Static Encephalopathy/Alcohol-Exposed (4-Digit Diagnostic Categories E,F). 3) ND/AE: Neurodevelopmental Disorder/Alcohol-Exposed (4-Digit Diagnostic Categories G,H). 4) Normal CNS/AE; No Central Nervous System abnormalities/Alcohol-Exposed (4-Digit Diagnostic Categories I,J). 5) Not FASD-alcohol exposure unknown or absent (4-Digit Diagnostic Categories D,K-,V). 6). Diagnosis Unknown (Survey submitted anonymously; patient identity and FASD diagnostic outcome on Survey unknown)[3].

TABLE 5. Summary of 395 Patient Follow-Up Surveys by 4-Digit Code FASD Diagnostic Classification: Access to Interventions and Needs Met

The value of a FASD diagnosis (2013)

Questions	Diagnostic Subgroups*													
	1. 14 FAS/ 29 PFAS		2. SE/AE		3. ND/AE		4. Normal CNS/AE		5. Not FASD		6. Diagnosis Unknown		Total	
	N = 43 (11%)		N = 92 (23%)		N = 132 (33%)		N = 27 (7%)		N = 39 (10%)		N=62 (16%)		N = 395	
	n	valid%	n	valid%	n	%	n	valid%	n	valid%	n	valid%	n	valid%
6. When you left Clinic, we recommended that you contact certain people and services to help you. How successful were you at finding these people and services?														
Very successful	17	45.9	38	55.1	58	55.2	10	55.6	17	56.7	24	53.3	164	53.9
Somewhat successful	16	43.2	26	37.7	36	34.3	4	22.2	10	33.3	17	37.8	109	35.8
Had very little success	4	10.8	3	4.3	6	5.7	2	11.1	2	6.7	2	4.4	19	6.3
Had no success at all	0	0	2	2.9	5	4.8	2	11.1	1	3.3	2	4.4	12	3.9
7. If you were able to find the people and services we recommended to you, were they able to meet your needs?														
Yes, they met all of my needs	13	44.8	26	53.1	39	51.3	6	42.9	8	40.0	14	42.4	106	48.0
Yes, they met some of my needs	15	51.7	21	42.9	34	44.7	7	50.0	11	55.0	19	57.6	107	48.4
No, they met none of my needs	1	3.4	2	4.1	3	3.9	1	7.1	1	5.0	0	0	8	3.6
8. Would you have liked the FAS Clinic to provide more help in finding community follow-up services or treatment?														
No	19	52.8	45	55.6	67	54.9	12	57.1	19	63.3	31	63.3	193	56.9
Yes	17	47.2	36	44.4	55	45.1	9	42.9	11	36.7	18	36.7	146	43.1

* 1) FAS/PFAS: fetal alcohol syndrome or partial FAS (4-Digit Diagnostic Categories A-C). 2) SE/AE: Static Encephalopathy/Alcohol-Exposed (4-Digit Diagnostic Categories E,F). 3) ND/AE: Neurodevelopmental Disorder/Alcohol-Exposed (4-Digit Diagnostic Categories G,H). 4) Normal CNS/AE; No Central Nervous System abnormalities/Alcohol-Exposed (4-Digit Diagnostic Categories I,J). 5) Not FASD-alcohol exposure unknown or absent (4-Digit Diagnostic Categories D,K-,V). 6). Diagnosis Unknown (Survey submitted anonymously; patient identity and FASD diagnostic outcome on Survey unknown).[3]

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The value of a FASD diagnosis (2013)

TABLE 6 Summary of 386 Patient Follow-Up Surveys by Patient Age at Time of 4-Digit Code FASD Diagnosis: Satisfaction and Confidence in Diagnostic Evaluation

Questions	0-2 Years			3-5 Years			6-12 Years			13-18 Years			19 + years			Total		
	N = 65 (17%)			N = 79 (20%)			N = 169 (44%)			N = 55 (14%)			N = 18 (5%)			N = 386		
Diagnosis*	n	valid%		n	valid%		n	valid%		N	valid%		n	valid%		n	valid%	
		row	col		row	col		row	col		row	col		row	col		row	col
FAS/PFAS	11	25.6	16.9	9	20.9	11.4	16	37.2	9.5	4	9.3	7.3	3	7.0%	16.7	43	100%	11.1%
SE/AE	8	8.7	12.3	15	16.3	19.0	48	52.2	28.4	15	16.3	27.3	6	6.5%	33.3	92	100%	23.8%
ND/AE	19	14.5	29.2	32	24.4	40.5	58	44.3	34.3	18	13.7	32.7	4	3.1%	22.2	131	100%	33.9%
Normal/AE	13	48.1	20.0	7	25.9	8.9	4	14.8	2.4	1	3.7	1.8	2	7.4%	11.1	27	100%	7.0%
Not FASD	3	7.7	4.6	6	15.4	7.6	20	51.3	11.8	9	23.1	16.4	1	2.6%	5.6%	39	100%	10.1%
Diagnosis Unknown	11	20.4	16.9	10	18.5	12.7	23	42.6	13.6	8	14.8	14.5	2	3.7%	11.1	54	100%	14.0%
2. Was the explanation of the evaluation:																		
Easy to understand	52		82.5	68		87.2	138		82.6	49		89.1	9		52.9	316		83.2
Somewhat complicated	11		17.5	10		12.8	29		17.4	6		10.9	8		47.1	64		16.8
Too complicated to understand	0		0	0		0	0		0	0		0	0		0	0		0
3. How much confidence do you have in the evaluation results?																		
A lot of confidence	60		93.8	69		87.3	150		89.3	46		83.6	15		88.2	340		88.8
Some confidence	3		4.7	10		12.7	14		8.3	9		16.4	1		5.9	37		9.7
Very little confidence	1		1.6	0		0	4		2.4	0		0	1		5.9	6		1.6
4. Did we provide information you needed and were unable to get elsewhere?																		
Yes	62		96.9	71		91.0	153		91.6	50		90.9	14		82.4	350		91.9
No	0		0	3		3.8	7		4.2	3		5.5	1		5.9	14		3.7
Uncertain	2		3.1	4		5.1	7		4.2	2		3.6	2		11.8	17		4.5
5. Did you feel your visit:																		
Took an appropriate amount of time	58		93.5	70		94.6	147		88.0	51		92.7	16		88.9	342		91.0
Was too short	2		3.2	3		4.1	16		9.6	3		5.5	1		5.6	25		6.6
Was too long	2		3.2	1		1.4	4		2.4	1		1.8	1		5.6	9		2.4
9. Would you recommend the FAS Clinic to other families with similar needs?																		
Yes	63		100	77		98.7	166		100	53		100	17		94.4	376		99.5

*FAS/PFAS: fetal alcohol syndrome or partial FAS (4-Digit Diagnostic Categories A-C). SE/AE: Static Encephalopathy/Alcohol-Exposed (4-Digit Diagnostic Categories E,F). ND/AE: Neurodevelopmental Disorder/Alcohol-Exposed (4-Digit Diagnostic Categories G,H). Normal CNS/AE; No Central Nervous System abnormalities/Alcohol-Exposed (4-Digit Diagnostic Categories I,J). Not FASD-alcohol exposure unknown or absent (4-Digit Diagnostic Categories D,K-,V). Diagnosis Unknown (Survey submitted anonymously; patient identity and FASD diagnostic outcome on Survey unknown)[3].

TABLE 7 Summary of 386 Patient Follow-Up Surveys by Patient Age at Time of 4-Digit Code FASD Diagnosis: Access to Interventions and Needs Met

Questions	0-2 Years		3-5 Years		6-12 Years		13-18 Years		19 + years		Total	
	N = 65 (17%)		N = 79 (20%)		N = 169 (44%)		N = 55 (14%)		N = 18 (5%)		N = 386	
	n	valid%	n	valid%	n	valid%	n	valid%	n	valid%	n	valid%
6. When you left Clinic, we recommended that you contact certain people and services to help you. How successful were you at finding these people and services?												
Very successful	30	60.0	32	52.5	74	54.4	20	47.6	7	50.0	163	53.8
Somewhat successful	15	30.0	24	39.3	46	33.8	17	40.5	3	21.4	105	34.7
Had very little success	3	6.0	1	1.6	13	9.6	4	9.5	2	14.3	23	7.6
Had no success at all	2	4.0	4	6.6	3	2.2	1	2.4	2	14.3	12	4.0
7. If you were able to find the people and services we recommended to you, were they able to meet your needs?												
Yes, they met all of my needs	25	62.5	24	58.5	44	45.8	9	26.5	3	33.3	105	47.7
Yes, they met some of my needs	14	35.0	16	39.0	51	53.1	22	64.7	4	44.4	107	48.6
No, they met none of my needs	1	2.5	1	2.4	1	1.0	3	8.8	2	22. 2	8	3.6
8. Would you have liked the FAS Clinic to provide more help in finding community follow-up services or treatment?												
No	37	64.9	41	57.7	79	52.7	29	64.4	6	42.9	192	57.0
Yes	20	35.1	30	42.3	71	47.3	16	35.6	8	57.1	145	43.0

Family Report of Access to Interventions and Needs Met by Interventions

Family's whose child received a 4-Digit Code diagnosis of SE/AE or ND/AE were as likely to report successfully accessing recommended interventions and having their needs met by the interventions as family's whose child received a diagnosis of FAS or PFAS (Table 5, Figure 3). Overall, 89% of families reported being somewhat to very successful in finding/accessing the recommended intervention services and 96% of those who found the services reported the services met some to all of their needs (Table 5). Access to interventions and having one's needs met by the interventions did not differ by diagnosis, but did differ by age (Table 7). Families of patients over 18 years of age reported less success finding and accessing recommended services and were less likely to report the interventions met their needs. A family's desire to receive more help from the Clinic to find services increased with increasing patient age.

Gestalt versus 4-Digit Code Method of Diagnosis

Among the 622 patients who returned their follow-up surveys, 227 (35%) were from patients who were diagnosed between 1993-1996 with the gestalt method of diagnosis and 395 (64%) were diagnosed between 1997 and 2012 with the 4-Digit Diagnostic Code. The survey outcomes for these two groups of patients are presented in Tables 8 and 9. Patients receiving a gestalt diagnostic evaluation were significantly less likely to report: 1) confidence in the outcome; 2) success in finding/accessing recommended intervention services, and 3) having their needs met by the services they accessed. The patient population evaluated from 1993-96, when the gestalt[24] method of diagnosis was in use, was slightly older than the patient population evaluated from 1997-2012, when the 4-Digit Code[3] method of diagnosis was used.

The value of a FASD diagnosis (2013)

TABLE 8 Summary of 622 Patient Follow-Up Surveys by Gestalt[24] versus 4-Digit Code Diagnostic Methods: Satisfaction and Confidence in Interdisciplinary Diagnostic Evaluation

Questions	Diagnostic System								
	Gestalt			4-Digit Code			Total		
	N =227 (36%)			N = 395 (64%)			N = 622		
	n	valid%		n	valid%		n	valid%	
1. Patient's age at time of diagnosis*		row	col		row	col		row	col
Birth to 2 years	19	22.6	8.4	65	77.4	16.8	84	100	13.7
3-5 years	54	40.6	23.8	79	59.4	20.5	133	100	21.7
6-12 years	79	31.9	34.8	169	68.1	43.8	248	100	40.5
13-18 years	55	50.0	24.2	55	50.0	14.2	110	100	17.9
19 or more years	20	52.6	8.8	18	47.4	4.7	38	100	6.2
2. Was the explanation of the evaluation:									
Easy to understand	189		84.4	318		83.2	507		83.7
Somewhat complicated	34		15.2	64		16.8	98		16.2
Too complicated to understand	1		0.4	0		0	1		0.2
3. How much confidence do you have in the evaluation results?**									
A lot of confidence	166		74.1	342		88.8	508		83.4
Some confidence	54		24.1	37		9.6	91		14.9
Very little confidence	4		1.8	6		1.6	10		1.6
4. Did we provide information you needed and were unable to get elsewhere?***									
Yes	192		90.1	352		91.9	544		91.3
No	19		8.9	14		3.7	33		5.5
Uncertain	2		.9	17		4.4	19		3.2
5. Did you feel your visit:									
Took an appropriate amount of time	193		86.9	343		91.0	536		89.5
Was too short	11		5.0	25		6.6	36		6.0
Was too long	18		8.1	9		2.4	27		4.5
9. Would you recommend the FAS Clinic to other families with similar needs?									
Yes	220		98.2	378		99.5	598		99.0

* Chi-square 24.2, 4df, p=0.000. **Chi-square 23.67, 2df, p=0.000. *** Chi-square 12.2, 2df, p=0.002.

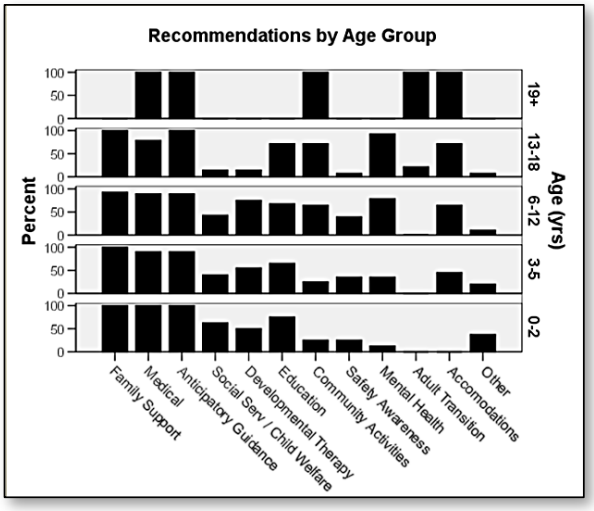
TABLE 9 Summary of 622 Patient Follow-Up Surveys by Gestalt[24] vs 4-Digit Code Diagnostic Methods: Access to Interventions and Needs Met

Questions	Diagnostic System*					
	Gestalt		4-Digit Code		Total	
	N =227 (36%)		N = 395 (64%)		N = 622	
	n	valid%	n	valid%	n	valid%
6. When you left Clinic, we recommended that you contact certain people and services to help you. How successful were you at finding these people and services?						
Very successful*	75	44.4	164	53.9	239	50.5
Somewhat successful	66	39.1	105	34.5	171	36.2
Had very little success	10	5.9	23	7.6	33	7.0
Had no success at all	18	10.7	12	3.9	30	6.3
7. If you were able to find the people and services we recommended to you, were they able to meet your needs?						
Yes, they met all of my needs**	47	36.2	106	48.0	153	43.6
Yes, they met some of my needs	69	53.1	107	48.4	176	50.1
No, they met none of my needs	14	10.8	8	3.6	22	6.3
8. Would you have liked the FAS Clinic to provide more help in finding community follow-up services or treatment?						
No	92	50.8	193	56.9	285	54.8
Yes	89	49.2	146	43.1	235	45.2

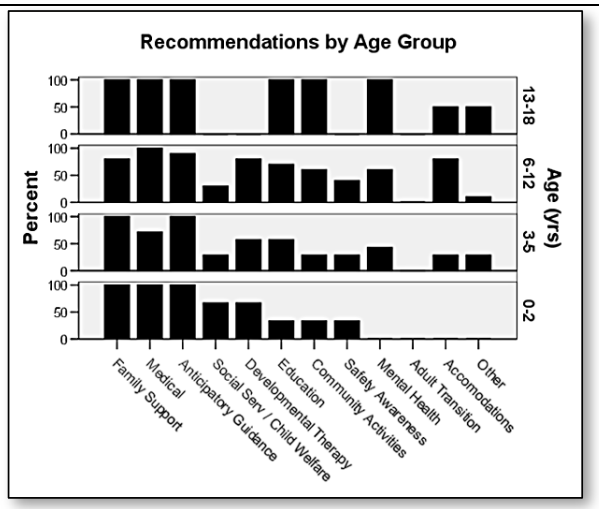
* Chi-square 10.7, 3df, p=0.013. ** Chi-square 9.6, 2df, p=0.008.

Profile of Intervention Recommendations by Age Group among Patients Diagnosed with the 4-Digit Code

Intervention recommendation profiles by age group are presented for two subsets of patients evaluated at the UW FASDPN clinic using the 4-Digit Code. Figure 4A illustrates the intervention profile for a representative sample of 170 of the 364 patients who had their interventions coded since 2007, when coding of interventions commenced at the UW FASDPN clinic. Figure 4B illustrates the intervention profile for the subset of 61 patients who returned Patient Follow-up Surveys. Both groups of patients have FASD diagnostic profiles that are comparable to (representative of) the larger population of all 395 patients diagnosed with the 4-Digit Code from which they were drawn. The diagnostic profile for the 170 patients in Figure 4A is: FAS/PFAS 15.2%, SE/AE 13.6%, ND/AE 53.0%, Normal CNS/AE 7.6%, Unknown 10.6%. The diagnostic profile for the 61 patients in Figure 4B is: FASPFAS 13.1%, SEAE 14.8, ndae 52.5, normAE 8.2%, Unknown 11.5%. These intervention profiles help put the Patient Follow-Up Surveys in perspective. When the patients were queried regarding their success at finding, accessing, and having their needs met by the interventions we recommended, the types of interventions they were pursuing are presented in Figure 4.



A



B

FIG. 4 Intevention recommendation profiles for two groups of patients who received FASD diagnostic evaluations at the Univeristy of Washington FASDPN clinic from 2007 to 2012 using the 4-Digit Code are presented. The bars represent the proportion of patients receiving each type of intervention by age group at the time of their diagnostic evaluation. **A**) Profile of intervention recommendations provided to a representative sample of 170 of the 364 patients evaluted from 2007 through 2012. **B**) Intervention profile for the 61 patients, from among the group of 170, who returned Patient Follow-up Surveys. The larger sample in Figure 4A demonstrates the profile among the subset of 61 who returned Patient Surveys is reflective of the larger population from which they were sampled. The twelve intervention subclassifications[17] are described in Table 1.

DISCUSSION

Patient follow-up surveys over 20 years illustrated the value of an interdisciplinary FASD diagnostic evaluation from an important perspective; the patient's perspective. Families (98%) expressed confidence in the interdisciplinary approach to diagnosis using the FASD 4-Digit Code with essentially all (99.5%) reporting they would recommend the diagnostic service to other families. The vast majority of families (89%) reported they were somewhat to very successful in finding/accessing the recommended intervention services and 96% of those who accessed the services reported the services met some to all of their needs. Patient reports that the recommended interventions "met some to all of their needs" is powerful qualitative evidence of intervention effectiveness and compliments the growing empirical, quantitative evidence-base on FASD intervention effectiveness.[33,34] It is important to clarify that patient outcomes over time were not directly measured in this study. When families/patients reported the interventions met some to all of their needs, the surveys did not document which specific needs were met. The intervention recommendations for each patient spanned the full continuum from services that directly addressed the patient's disabilities to services that provided caregivers with advocacy training, education, resources, even respite care (Table 1). Thus, when families report their needs were met, this is certainly a positive outcome and reflects just one of many ways to assess intervention effectiveness, but does not replace the need for more direct, empirical assessments of improved patient outcome.

The results of this study document a FASD diagnostic evaluation helped break down some of the treatment barriers and unmet needs often reported by caregivers.[35-38] Families report that these unmet needs are one of the primary reasons they are seeking an evaluation in our clinic. They typically report having received evaluations and services from a large array of providers prior to attending our clinic. Nevertheless, 92% report we provided them with information they were unable to obtain elsewhere despite the fact the clinic is located in a large metropolitan area (Seattle) with many genetic, neurodevelopmental, and psychological evaluation services available. This single 4-hour interdisciplinary evaluation appears to provide more information and access to services than the multitude of uncoordinated services the families reported accessing prior to coming to our clinic. The potential cost savings of this more efficient and more effective interdisciplinary approach to meeting these family's complex needs is enormous and will be the focus of a separate report.

Patients with Neurobehavioral Disorder/Alcohol-Exposed (ND/AE) and Static Encephalopathy/Alcohol-Exposed (SE/AE) were as successful accessing interventions that met their needs as patients with FAS or PFAS. This is in contrast to the oft stated belief that a patient will not qualify for services if the diagnosis is not FAS, PFAS or at least given a name that implies alcohol is the causal agent (e.g., Alcohol-Related Neurodevelopmental Disorder (ARND)). The FASD 4-Digit Code does not use the term Alcohol-Related Neurodevelopmental Disorder because one cannot confirm an individual's neurodevelopmental disorder is related to their prenatal alcohol exposure in the absence of the FAS facial phenotype. This study demonstrated that the diagnostic labels SE/AE and ND/AE were as effective as FAS and PFAS in providing access to intervention services. This is encouraging since individuals should qualify for services based on their disability, not on what caused their disability.

Several factors likely contributed to our patients' success in finding and accessing the recommended interventions. Access to services requires more than a diagnostic label. The diagnostic labels FAS, PFAS, SE/AE and ND/AE reveal the magnitude of disability, but do not reveal the individual's specific pattern of disability. No two individuals on the spectrum of FASD necessarily present with the same pattern of disability[8,39], and their unique pattern of disability manifests differently over their lifetime. For this reason, the most important component of the FASD interdisciplinary diagnostic evaluation is a current, comprehensive developmental /neuropsychological assessment. The outcomes of

this assessment not only help derive the diagnostic classification, but provide the core information that ultimately drives the intervention plan and qualifies an individual for services.

For a patient to derive the greatest benefit from their FASD diagnostic evaluation, they need an interdisciplinary team that can: 1) render an accurate diagnosis under the umbrella of FASD; 2) generate a comprehensive intervention plan tailored to their specific needs and circumstances; and 3) present all of this in a comprehensive medical summary report that effectively informs and educates the family and their community service providers. Over the last 20 years, the UW FASDPN interdisciplinary team has gained considerable expertise and experience in meeting the needs of this patient population. Most of the clinicians have served on the team for more than 10 years, with several having served the entire 20 years. Two factors that have contributed tremendously to the team's ability to work efficiently and effectively include: 1) their creation of an up-to-date, comprehensive list of over 200 intervention recommendations key-coded into an Intervention Plan template and 2) their creation of the FASD Medical Summary Report template. Both Microsoft Word templates are available to clinicians at no cost through the WA FASDPN. The Intervention Plan template allows the team to construct a detailed, customized list of interventions that not only meet the patient's needs, but are known to be available in the patient's community, and are likely to be financially accessible to the patient. The intervention plan spans the full continuum of patient and caregiver needs from medical, educational, placement, social service, even caregiver respite.[17] The intervention plan is printed and handed to the family at the conclusion of their 4-hour appointment. The FASD Medical Summary Report is a single, comprehensive, interdisciplinary report composed by the interdisciplinary team members. During the 4-hour appointment, team members sit at one of several computer stations, log into their report template and compose a brief report summarizing which assessments they administered, the outcomes of the assessments, and their interpretation of the outcomes. Each of these electronic reports is collected at the end of the 4-hour evaluation and inserted into the FASD Medical Summary Report template by the clinic coordinator. The FASD Medical Summary Report is complete within one hour following the 4-hour evaluation. The Intervention Plan is merged with the Medical Summary report and submitted to the patient's medical record and mailed to the patient's legal guardian within one week of their diagnostic evaluation.

The FASD Medical Summary Report is designed to both educate and inform the patient and their care providers. The content and format of this report is vital to a patient's success in accessing intervention services. A medical summary that conveys a rigorous diagnostic process and includes the assessment outcomes that ultimately drove the intervention recommendations will go far to earn the respect of the professional community. Our FASD Medical Summary Report: 1) outlines the interdisciplinary process used to derive the diagnosis, 2) describes how the 4-Digit Code measures the magnitude of impairment across the four components that characterize FASD (growth deficiency, FAS facial phenotype, CNS abnormalities, and prenatal alcohol exposure), 3) presents the patient's outcomes in each of these four areas, 4) provides a diagnostic classification with brief description, and 5) concludes with a comprehensive intervention plan. In the words of one caregiver of a 10 year old who received a diagnosis of SE/AE "*I cannot say enough good things about your services. A proper diagnosis has resulted in: change of school placement, OT/PT services provided by the school district, a referral to mental health in hopes of finding a therapist w/background in neurodevelopmental problems and patient's psychiatrist reducing his medications*".

Families of patients who were birth to 5 years of age at the time of diagnosis reported the greatest access to recommended interventions that met their needs. The WA FASDPN clinics have been accurately and effectively diagnosing individuals across the entire age span for 20 years. The youngest and oldest patients to date were 2 days old and 53 years old, respectively. One third of the WA FASDPN patient population is birth to

5.9 years of age at the time of diagnosis.[8] Their outcomes span the full continuum of FASD diagnoses. Of the 760 patients (birth to 5.9 years of age) with confirmed prenatal alcohol exposures evaluated in the first 20 years, 13% were diagnosed with FAS/PFAS; 19% with SE/AE, 51% with ND/AE; and 18% with No CNS Abnormalities/AE. Not only is an accurate FASD diagnostic evaluation possible in this young age group, but according to this study, highly beneficial. This is the age group with the greatest access to services and the greatest potential to benefit from the services.[18] This is also the age group that can lead to the most successful primary prevention efforts by reaching out to their birth mothers early in their reproductive history to prevent alcohol exposure in subsequent births.[11,12] Adult patients (19 years of age or older) reported less success (71%) finding and accessing recommended interventions relative to younger age groups (90%). Adults were also less likely (77%) to report the services met their needs compared to the younger age groups (98%). Reports of less access to and benefit from intervention services are reflective of the paucity of services available to adults with disabilities. The primary reason adult patients report seeking an FASD evaluation is the hope that the outcome will qualify them for Supplemental Security Income (SSI) or developmental disabilities assistance. Qualification for these forms of assistance in WA State is based in large part on FSIQ and adaptive behavior performance more than 2 standard deviations below the mean. Most of the adults receiving a diagnosis under the umbrella of FASD, including full FAS, do not present with FSIQs below 70. We are working with our State policy makers to address this issue.

CONCLUSION

Patient surveys over 20 years confirm an interdisciplinary diagnosis using the FASD 4-Digit Diagnostic Code provides substantial access to interventions that meet patients' needs across the full spectrum of FASD diagnoses. This is powerful evidence of the value of an FASD diagnostic evaluation.

Acknowledgments

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BMC Pediatrics

COMMENTARY Open Access

Invited commentary on Australian fetal alcohol spectrum disorder diagnostic guidelines

Susan J Astley

Abstract

The publication of Australian fetal alcohol spectrum disorder (FASD) diagnostic guidelines marks an important step forward in Australia's efforts to prevent FASD. But do we need yet another set of FASD guidelines? At the 5th International FASD Conference, the ever growing number of FASD diagnostic guidelines was identified as a core area of concern by leaders in FASD worldwide. All agreed we need to strive to adopt a single set of guidelines. It is essential that FASD diagnosis advance to incorporate new knowledge and technology. But to date, the field of FASD has seen multiple sets of guidelines published that do not address the important question-*How is the performance of these new guidelines superior to the performance of existing guidelines to warrant/justify their introduction into the medical literature*?

The Australian guidelines include FAS, PFAS and Neurodevelopmental Disorder-Alcohol Exposed (ND-AE). This latter group includes individuals with severe CNS abnormalities without the physical features of FAS. This is the group the 4-Digit-Code calls Static-Encephalopathy-Alcohol-Exposed (SE-AE). The criteria for FAS, PFAS, and ND-AE (or what the 4-Digit-Code calls SE-AE) are identical between the Australian and 4-Digit-Code guidelines with the exception of one very small, but very consequential difference in facial criteria for PFAS. The 4-Digit-Code requires a Rank 3 FAS facial phenotype for PFAS (*J Popul Ther Clin Pharmacol* **20**(3):e416–e467, 2013); the Australian guidelines relax the criteria to include the Rank 2 FAS facial phenotype. This relaxation of the criteria renders the facial phenotype NOT specific to prenatal alcohol exposure as confirmed in published empirical studies. If the facial phenotype is not specific to (caused only by) prenatal alcohol exposure one can no longer validly call the outcome PFAS. When one makes a diagnosis of FAS (full or partial), one is stating explicitly that the individual has a syndrome caused by prenatal alcohol exposure. One is also stating explicitly that the biological mother drank alcohol during pregnancy and, as a result, harmed her child. These are bold conclusions to draw and are not without medical, ethical, and even legal consequences. So the question remains-Why go against the published empirical evidence and relax the PFAS facial criteria into the normal range?

Keywords: Fetal alcohol spectrum disorders, FASD 4-digit diagnostic code

The publication of Australian fetal alcohol spectrum disorder (FASD) diagnostic guidelines [1] marks an important step forward in Australia's efforts to prevent FASD. Accurate identification of the full spectrum of outcome caused by prenatal alcohol exposure is central to FASD screening, diagnosis, intervention, surveillance, and ultimately prevention [2,3]. But do we need yet another set of FASD guidelines?

FASD diagnostic guidelines have evolved over time since the term FAS was first coined in 1973 [4]. Early guidelines were gestalt (purposely broad and conceptual) in nature and administered primarily by geneticists/dysmorphologists. The 1996 Institute of Medicine FASD guidelines [5] would be the last in this line of gestalt approaches to diagnosis. In 1997, the FASD 4-Digit-Diagnostic-Code was introduced to overcome the limitations (inaccuracies) of the gestalt method of diagnosis [6-8]. The 4-Digit-Code introduced an interdisciplinary approach guided by rigorously and empirically case-defined criteria. When the 4-Digit-Code was introduced into the medical literature, it was presented in the form of an empirical study demonstrating its superior performance to the gestalt approach it proposed to replace [7]. Over the next 17 years,

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it performance would continue to be extensively assessed (validated [2,9]) through MRI studies [10], population-based screening/surveillance studies [11-14], and patient follow-up surveys [15]. Between 2004 and 2013, five additional FASD diagnostic guidelines will be introduced into the literature [16-19]. All proposed an interdisciplinary approach using defined criteria. Most were established through a consensus process, but none had performance assessed (validated) prior to or even after publication. Most present with criteria that are marginally different from the 4-Digit-Code, but none provide empirical evidence demonstrating their superior performance relative to existing guidelines. It is essential that FASD diagnosis advance to incorporate new knowledge and technology. But to date, the field of FASD has seen multiple sets of guidelines published that do not address the important question-*How is the performance of these new guidelines superior to the performance of existing guidelines to warrant/justify their introduction into the medical literature* [2]? At the 5th International FASD Conference in 2013, the ever growing number of FASD diagnostic guidelines was identified as a core area of concern by leaders in FASD worldwide. All agreed we need to strive to adopt a single set of guidelines.

The most recent guidelines introduced into the literature are the Australian guidelines [1]. More accurately, they are consensus recommendations providing a foundation for development of Australian FASD diagnostic guidelines. The Australian guidelines adapted elements of the 4-Digit-Code and Canadian Guidelines. Let's take a closer look.

The Australian guidelines include FAS, PFAS and Neurodevelopmental Disorder-Alcohol Exposed (ND-AE). This latter group includes individuals with severe CNS abnormalities without the physical features of FAS. This is the group the 4-Digit-Code calls Static-Encephalopathy-Alcohol-Exposed (SE-AE). The Australian guidelines chose not to use the term Alcohol-Related-Neurodevelopmental-Disorder (following the 4-Digit Code and DSM-5 [20] conventions) due to the implication of causality between exposure and outcome that cannot be confirmed. The criteria for FAS, PFAS, and ND-AE (or what the 4-Digit-Code calls SE-AE) are identical between the Australian and 4-Digit-Code guidelines with the exception of one very small, but very consequential difference in facial criteria for PFAS. The 4-Digit-Code requires a Rank 3 FAS facial phenotype ("2.5" of the 3 facial features must be present) for PFAS; the Australian guidelines relax the criteria to include the Rank 2 FAS facial phenotype (2 of the 3 facial features). This relaxation of the criteria renders the facial phenotype NOT specific to prenatal alcohol exposure as confirmed in published empirical studies [2,3,21,22]. In one of those studies 25% of a group of high-functioning (mean IQ 120) children with confirmed absence of prenatal alcohol exposure presented with 2 of the 3 features. This study clearly demonstrated that the PFAS facial phenotype proposed in the Australian guidelines is not observed exclusively among children damaged by prenatal alcohol exposure. If the facial phenotype is not specific to (caused only by) prenatal alcohol exposure (and we already know the growth and CNS abnormalities are not caused only by prenatal alcohol exposure) one can no longer validly call the outcome PFAS. This problem is not resolved by requiring a confirmed prenatal alcohol exposure. The problem lies in the name (PFAS) given to the condition. When one makes a diagnosis of FAS (full or partial), one is stating explicitly that the individual has a syndrome caused by prenatal alcohol exposure. One is also stating explicitly that the biological mother drank alcohol during pregnancy and, as a result, harmed her child. These are bold conclusions to draw and are not without medical, ethical, and even legal consequences. If the growth, face and CNS criteria for PFAS are not specific to prenatal alcohol exposure, a clinical team is in no position to claim the child has a condition caused by their mother‟s alcohol use. A second problem arises with the relaxation of the facial features for PFAS into the normal range (requiring only 2 of the 3 features). If the facial criteria are relaxed, the Australian PFAS group is no longer clinically distinct from the Australian ND-AE group [2,3]. Note the only feature that distinguishes the Australian PFAS group from their ND-AE group is the facial criteria. But if the facial criteria for PFAS are relaxed into the normal range, the facial criteria are no longer clinically distinct from the facial criteria for ND-AE. If there is no clinically meaningful distinction between PFAS and ND-AE, what is the justification for creating two separate diagnostic subgroups? So the question remains-Why go against the published empirical evidence and relax the PFAS facial criteria into the normal range?

The Australian guidelines report the UW 4-Digit-Code could also be derived if desired". Unfortunately, the only issue preventing clinicians from deriving a 4-Digit-Code that would be in complete compliance with the Australian guidelines is the relaxation of the PFAS facial criteria from a Rank 3 to a Rank 2. If the Australian guidelines required a Rank 3 face for PFAS, it would not only gain the specificity required to validate the use of the term PFAS, but the 4-Digit-Codes would derive 4-Digit clinical categories (FAS, PFAS, SE-AE) that match the Australian clinical categories (FAS, PFAS, ND-AE). If the 4-Digit-Code said it was FAS, so would the Australian guidelines. If the 4-Digit-Code said it was PFAS, so would the Australian guidelines. And if the 4-Digit-Code said it was SE-AE, so would the Australian guidelines (but the Australian guidelines would simply give it a different label (ND-AE)). Individuals who present with moderate CNS dysfunction (what the 4-Digit-Code calls Neurobehavioral-Disorder-Alcohol-Exposed) would receive 4-Digit-Codes documenting

their outcomes, but in accordance with the Australian guidelines would not receive a label. This would seem a reasonable interim solution as Australians further assess how to handle this moderate end of the FASD spectrum. The authors report "*Although there is an extensive evidence base confirming prenatal alcohol exposure causes the full range of outcomes from moderate to severe CNS dysfunction and a growing evidence base documenting significant CNS structural abnormalities among alcohol-exposed individuals with moderate dysfunction; panel members identified the need for additional evidence to more fully evaluate the validity of diagnosis based on moderate CNS dysfunction*" Rendering a 4-Digit-Code would allow one to quickly apply a label retroactively in the event Australia elects to recognize (e.g., label) this moderate end of the FASD spectrum in the future.

Response

Rochelle E Watkins, Elizabeth J Elliott, Janet M Payne, Colleen M O'Leary, Jane Halliday, Jane Latimer, Amanda Wilkins, Raewyn C Mutch, James P Fitzpatrick, Heather M Jones, Lorian Hayes, Heather D'Antoine, Sue Miers, Elizabeth Russell, Lucinda Burns, Anne McKenzie, Maureen Carter, Carol Bower.

We have recently published recommendations for the diagnosis of fetal alcohol spectrum disorders (FASD) in Australia. These recommendations seek to address the known issue of underdiagnosis through supporting improved awareness of FASD and increased national capacity to respond to, and ultimately prevent, these disorders. We used an adaption approach to guideline development in recognition of existing diagnostic guidelines. Recommended national standard diagnostic criteria for Australia are based on the University of Washington (UW) 4-Digit Diagnostic Code and Canadian guidelines for FASD diagnosis. Our conclusions emphasise the importance of evaluation to improve the evidence-base for policy and practice.

In her commentary on our recommendations, Astley has raised important questions about the publication of this work, including whether we need 'yet another guideline', and expressed concern about the recommended criteria for the diagnosis of partial fetal alcohol syndrome (PFAS). Guideline development is a recognised and widely used mechanism to influence clinical practice. The lack of guidelines for diagnosis in Australia has been identified as one of the factors contributing to the underdiagnosis of FASD. We sought to establish the basis for a standard national approach to diagnosis in Australia through the adoption or adaption of existing guidelines.

Existing diagnostic guidelines lack agreement on all aspects of diagnosis, and the recommended diagnostic criteria for PFAS remain subject to debate. Although our recommended diagnostic criteria for PFAS in Australia based on the presence of 2 characteristic facial features differ from the UW guidelines, they lie within the range of criteria recommended by other guidelines. We sought peer review and publication of our findings to provide transparency and promote awareness of our work nationally and internationally. We support international collaboration to develop a common approach to diagnosis, and believe that this process will strengthen the evidence base for action globally.

Background

North America leads the world in the production of guidelines for the diagnosis of fetal alcohol spectrum disorder (FASD), and these provide a rich resource for those seeking to address and prevent the harm caused by prenatal exposure in other contexts. We recently published Australian recommendations for FASD screening and diagnosis [1] with the aim of supporting clinical decision-making to improve the identification, management and prevention of these disorders based on a standard national approach. In her commentary on our recommendations, Astley has raised some important questions about the need for these guidelines, the publication of this work and the recommended criteria for the diagnosis of partial fetal alcohol syndrome (PFAS).

National focus

The development of clinical practice guidelines has been identified as a critical activity at the national level to facilitate the delivery of effective health services [23]. The majority of published guidelines for the diagnosis of FASD were commissioned by government health agencies and motivated by concern about the impact of prenatal alcohol exposure at a national level. It is unlikely to be coincidental that North America has both published the greatest number of guidelines for diagnosis and gained recognition as leading the world in many aspects of FASD practice and research.

Guidelines are developed with the aim to influence practice. They need to be locally appropriate and integrated with strategies to facilitate their implementation. High quality guidelines developed at the international level can facilitate the development of locally appropriate guidelines for specific practice settings and, increasingly, local health providers are developing methods to integrate evidence in their own settings [24]. The need to improve service delivery and support health professionals' capacity to diagnose FASD in Australia [25,26] underpinned the Australian Government's call for development of a diagnostic instrument for Australia. The absence of guidelines for FASD diagnosis in Australia has been linked to underdiagnosis [27] and inaccurate FASD prevalence estimates [28]. The lack of a national standard approach undermines the effectiveness of interventions to educate

health professionals, increase diagnostic and management capacity, and conduct surveillance and evaluation.

Adoption or adaption

Through the development of national recommendations for FASD screening and diagnosis we aimed to improve awareness of FASD and strengthen national capacity to identify, address and prevent the harms associated with alcohol consumption in pregnancy. Four key factors framed our approach: i) that there are no international consensus criteria for diagnosis; ii) that there is variation in diagnostic practices internationally [29]; iii) that the most recent guidelines were published in 2005, and none with a published formal review; and iv) that there was little evidence to support the natural emergence of any standard national approach to diagnosis in Australia.

A range of existing guidelines have been used for diagnosis in Australia. The Institute of Medicine criteria [5] were used in the first national surveillance study in 2001 [30], the Canadian guidelines [17] were used in the first national prevalence study in 2009 [31], and the University of Washington (UW) 4-Digit Diagnostic Code [8] has been proposed for national use by authors examining the issues of diagnostic capacity and surveillance [27,28].

We used an adaption approach to development [32] in recognition of existing guidelines for diagnosis, and our work followed the accepted process of identifying whether existing guidelines would be adopted or adapted for local use [33] within a recognised research framework [34,35]. We found no clear support for the adoption of any single existing guideline [1,26]. Our recommendations have been developed to provide the foundation for a coordinated national approach to service provision, and are based on the cornerstone contributions of existing diagnostic guidelines that have helped to advance practice globally.

Process and judgement

There are considerable challenges in producing evidence-based guidelines for FASD screening and diagnosis, and disagreement between guidelines can arise for various reasons, not all of which imply that different recommendations are invalid [36]. We developed recommendations for Australia based on the deliberations of a range of stakeholders within a consensus-based approach. As is often the case in guideline development, there was a recognised need to move beyond the limited research evidence [37], and rarely 'an abundance of evidence available that leads directly to an indisputable recommendation' [38] p. 35. Recommendation development is a largely qualitative process with the need to consider multiple factors and considerable potential to encounter differences in judgement for a number of reasons, including perceptions about relevance, feasibility, risks and benefits. Panel members noted the need for additional evidence to evaluate differences in recommendations between existing guidelines, as well as the recommendations developed for Australia [1].

In the specific case of differences between the UW and Australian recommendations with respect to the facial features required for a diagnosis of PFAS, the panel recognised that the criteria for the diagnosis of PFAS remain subject to debate [39,40]. Diagnosis of disorders within the FASD spectrum is consistently challenged by an insufficient understanding of factors which contribute to individual susceptibility and phenotypic variability, and research highlights both the clinical significance of facial abnormalities [41,42] and the potential for variation in facial dysmorphology [43,44]. We support the need for further research to examine the validity of recommended diagnostic criteria for PFAS and facilitate international consensus in this area, and believe it would be premature to conclude that the diagnostic category of PFAS based on the presence of 2 facial features is invalid at this time.

Recommended facial criteria for the diagnosis of PFAS in Australia are consistent with existing guidelines [17,18], and differences in categorisation between the UW and other guidelines do not result in substantial differences in outcomes such as a diagnosis on the spectrum where one would otherwise have not been made. With reference to the potential harm caused by a diagnosis of PFAS using the recommended Australian criteria, we do not claim causation in the case of PFAS when diagnosed based on the presence of 2 characteristic facial features. The use of a non-causal assumption could be considered more conservative than assuming causation where specificity is known to be less than 100%. Contrary to Astley's comment, sufficient detail is recorded during the recommended assessment process to enable derivation of the 4-Digit Diagnostic Code despite differences between the diagnostic categories recommended in Australia and the UW guidelines. Further evaluation is critical to validating diagnostic criteria, and ensuring that the diagnostic categories used are based on meaningful distinctions across the spectrum.

We believe that our work provides a credible basis for advancing practice in Australia and, consistent with the purposes of the scientific literature and the need for transparency in recommendation development, we sought peer review and publication of a research paper which documents the methods used to develop these recommendations. If, through seeking peer review and publication to promote national and international awareness of our goals and progress, this process highlights broader issues that confront the development of FASD guidelines internationally, then we have achieved more than we had hoped.

Competing interests

The author declares that she has no competing interests.

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Recommendations from the

Washington State

Fetal Alcohol Spectrum Disorders (FASD) Interagency Work Group

December 2014

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Please forward comments/questions to:
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An electronic version of this report is posted on the WA FASD-IAWG website.
http://depts.washington.edu/fasdwa/PDFs/FASD-IAWG-Dec2014-Report.pdf

EXECUTIVE SUMMARY

This report was written in response to a component of House Bill 2737 (introduced in January, 2014; did not pass) concerning Fetal Alcohol Syndrome (FAS) and Fetal Alcohol Spectrum Disorders (FASD). FAS is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. FASD is the name for the full spectrum of damage caused by prenatal alcohol exposure. FAS and FASD are 100% preventable. The purpose of this report is to describe the problem in Washington State, identify evidence-based practices for early screening, diagnosis, prevention, and intervention, and recommend policy changes.

The report draws attention to the fact that in Washington State an estimated 870 children are born with FASD each year (1% of all births), and approximately 70,000 individuals with FASD of all ages currently live here. FASD is the leading known cause of intellectual disabilities, its primary impact is on schools, foster and adoption services, the justice system, and mental health services; fewer than 10% of adults with FASD live independently or remain employed. It costs an estimated 2 million dollars in lifetime social and health care services for every child born with FASD. Annual Medicaid costs are 9 times more annually for a child with FASD compared to a child without FASD. It costs 30 times more to raise a child with FASD than to prevent FASD in the child.

The report highlights the substantial contributions made by clinicians and researchers in Washington State to developing evidence-based practices recognized and replicated globally to address FASD. These include screening, diagnosis and surveillance contributions. The University of Washington FAS Diagnostic & Prevention Network (FASDPN) clinic introduced the interdisciplinary approach to FASD diagnosis in 1992 and developed rigorous, validated tools (the FASD 4-Digit Diagnostic Code and FAS facial recognition software) to improve diagnostic accuracy. These tools and clinical model have been adopted worldwide and serve as the cornerstone for FAS screening in Washington's foster care system. FAS screening serves the dual purpose of identifying children at risk and tracking FAS prevalence over time. FAS screening has confirmed 1 out of every 100 children in Washington's foster care system has FAS. FAS screening has also confirmed the prevalence of FAS decreased significantly in Washington State as did maternal drinking during pregnancy, documenting Washington State's FASD prevention efforts are working, It "takes a village" to prevent FASD. The University of Washington FASDPN has trained thousands of healthcare, educational, correctional, and social service providers about the integral role they play in our ongoing, statewide effort to prevent FASD. The report also describes the widely-replicated, and highly successful FASD prevention model, the Parent-Child Assistance Program (PCAP). PCAP works with women who are at highest risk for delivering children with FASD, and demonstrates consistently positive research outcomes and significant cost savings for Washington State. Evidence-informed intervention best practices are also described, based on over two decades of research conducted at the University of Washington (e.g. studies of risk and protective factors for adverse life outcomes associated with FASD; the utility of

neuropsychological assessments in helping adults with FASD; Families Moving Forward with FASD, a clinician-guided intervention model meeting the needs of families affected by FASD).

Although Washington's prevention efforts are working, the State's capacity to screen, diagnose, treat, and prevent FASD falls far below the statewide need/demand for such services (e.g., the current average wait time for a family seeking a FASD diagnostic evaluation is 9 months). The report makes the following key recommendations:

Screening and Diagnosis of FASD

- Maintain current diagnostic capacity for the core University of Washington FASDPN Clinic, and if possible increase FASD diagnostic capacity through the FASDPN Network Clinics.
- Increase capacity for neuropsychological assessment of adults on Medicaid.
- Educate clinicians statewide on the importance of screening for and documenting prenatal alcohol exposure.

Prevention of FASD

- Maintain current PCAP funding in eleven counties and if possible expand PCAP to additional counties that have high rates of prenatal substance abuse, such as Thurston.
- Increase residential and outpatient substance abuse treatment capacity for pregnant and parenting women across the state.
- Increase distribution of the WA Department of Health "Substance Abuse During Pregnancy: Guidelines for Screening and Management".

Interventions for Individuals with FASD

- Reinstate funding support for community advocacy groups like NOFAS WA.
- Increase the capacity of intervention programs like Families Moving Forward.

Policy Changes to Improve FASD Identification, Prevention, and Intervention

- Explore all available opportunities to diversify funding sources, including maximizing federal Medicaid funding in order to reduce the fiscal impact on state general funds.
- Revise Developmental Disability Administration (DDA) eligibility criteria so that applicants with FASD, not just those with FAS, can be considered for eligibility under "another neurological or other condition.

INTRODUCTION

House Bill 2737 concerning Fetal Alcohol Exposure **(Appendix A)** was introduced on January 29, 2014 and was referred to Early Learning & Human Services. A public hearing in the House Committee on Early Learning & Human Services was held on February 13, 2014. This bill proposed the WA Fetal Alcohol Spectrum Disorder Interagency Work Group (FASD-IAWG) develop recommendations and provide a report by December 2014 to the appropriate committees of the legislature relating to:

- Identification of evidence-based practices for early screening and diagnosis of fetal alcohol spectrum disorders (FASD);
- Identification of evidence-based practices for prevention of FASD;
- Identification of evidence-based practices for interventions that can be used with individuals experiencing FASD; and
- Recommendations of policy changes that would improve the identification, prevention, or interventions related to FASD.

Although the bill did not pass, the FASD-IAWG made a commitment to produce the report requested in the draft legislation.

MEMBERSHIP

The Fetal Alcohol Spectrum Disorders Interagency Work Group (FASD-IAWG) was first established in 1995 through Substitute Senate Bill 5688 **(Appendix B)**. Senate Bill 5688 stipulated "*The department of social and health services, the department of health, the department of corrections, and the office of the superintendent of public instruction shall execute an interagency agreement to ensure the coordination of identification, prevention and intervention programs for children who have fetal alcohol exposure, and for women who are at high risk of having children with fetal alcohol exposure*." The FASD-IAWG has been meeting biannually since 1995. Its mission and accomplishments are presented on its website fasdwa.org. The agenda for 2014 was to develop and advance recommendations concerning FASD and summarize these recommendations in a December 2014 Report for distribution to appropriate committees of the legislature.

The 2014 FASD-IAWG is co-chaired by the FASD State Coordinator from DSHS (Sarah Pine), the director of the University of Washington Fetal Alcohol Syndrome Diagnostic and Prevention Network (Susan Astley, Ph.D.), and the director of the University of Washington Fetal Alcohol and Drug Unit (Therese Grant, Ph.D.). The Work Group includes several clinicians from the University of Washington FASD Diagnostic Clinic, the director of the University of Washington FASD Legal Issues Resource Center, a FASD Educator, the Director of NOFAS WA, and a young adult with FAS. Other members include the Assistant Secretary of DSHS/BHSIA, and representatives from DOH, DOC, and OSPI. A list of the individuals who served on this Work Group can be found in **Appendix C.**

2014 MEETINGS

The Working Group conducted meetings on the following dates:

June 12, 2014; September 15, 2014; October 29, 2014; December 1, 2014

WORK GROUP MEETING RECORDS

Please note that minutes from each meeting of the Work Group are available by contacting Sarah Pine, FASD State Coordinator.

BACKGROUND

Work Group members felt it necessary to provide the following background on fetal alcohol spectrum disorders in Washington State to serve as a basis for the recommendations which follow.

What is FAS and FASD and How is it Diagnosed?

Fetal alcohol syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. FAS is characterized by growth deficiency, brain damage, and a unique cluster of facial features. Not all children exposed to and damaged by alcohol during gestation are born with FAS. Most are born with brain damage, but do not have the unique facial features of FAS. These children need the same social, educational, and healthcare services as children with FAS and far outnumber, by 10 to 1, children with FAS. The full spectrum of damage caused by prenatal alcohol exposure is called Fetal Alcohol Spectrum Disorders (FASD). There are four diagnoses under the umbrella of FASD.

Four Diagnoses under the Umbrella of FASD						
Diagnosis		Growth	FAS Face	Brain		Alcohol
1. FAS	Fetal Alcohol Syndrome	growth	face	severe		alc
2. PFAS	Partial FAS		face	severe		alc
3. SE/AE*	Static Encephalopathy / Alc Exposed			severe		alc
4. ND/AE	Neurobehavioral Disorder / Alc Exposed				moderate	alc

* Also referred to as:
- Alcohol Related Neurodevelopmental Disorder (ARND) or
- Neurodevelopmental Disorder Prenatal Alcohol Exposed (ND-PAE)

Diagnosis of FASD is conducted by an interdisciplinary team using evidence-based diagnostic guidelines. This diagnostic model was first introduced by the University of Washington in 1993 and has been adopted as best practice worldwide (SAMHSA, 2014). An interdisciplinary team of clinicians (medical doctor, psychologist, speech language pathologist, occupational therapist, social worker, and family advocate) is required to diagnosis FASD because the damage caused by prenatal alcohol exposure impacts all aspects of an individual's growth and brain development. The expertise of a medical doctor is required to assess the physical and neurological components of the disorder (i.e., growth deficits, facial anomalies, seizures). The expertise of a psychologist, speech language pathologist, and occupational therapist is required to assess the brain function component of the disorder. Deficits occur across multiple domains of brain function including attention, cognition, memory, language, and motor skills. The collective expertise of this team is also required to generate an effective, comprehensive intervention plan. The WA FASDPN conducts an FASD diagnostic evaluation in one 4-hour appointment using the FASD 4-Digit Code (Astley, 2004). The patient receives an accurate diagnosis and comprehensive intervention plan at the end of the 4-hour appointment and receives a 12-page comprehensive medical summary report the following week.

What is the Fiscal Impact of FASD on Washington State?

- It costs an estimated 2 million dollars in lifetime social and health care services for every child born with FASD (Lupton et al., 2004; Thanh & Jonsson, 2009). 870 children with FASD are born each year in Washington State (SAMHSA, 2006)
- In 2005 it cost Medicaid 9 times more in annual medical expenditures to care for a child with FASD than to care for a child without FASD ($16,782/child/year vs. $1,859/child/year) (Amendah et al., 2011). For comparison, it cost Medicaid $10,709/child/year to care for a child with Autism Spectrum Disorder.
- Washington State is the only place in the world that has successfully reduced the prevalence of maternal drinking during pregnancy statewide (14% to 4%), and documented that reduction in drinking correlated with a significant decrease in the birth rate of FAS in high-risk foster care (6% to 2%) (Astley, 2004). This was achieved within 5 years of opening two world-renowned, evidence-based programs supported in part through RCW 70.96A.500:
    1. The Fetal Alcohol Syndrome Diagnostic & Prevention Network (FASDPN)
    2. The Parent-Child Assistance Program (PCAP).
- With the combined efforts of these programs, it costs 30 times less to prevent FASD in a child, than to raise a child with FASD (Astley et al., 2000).
- Among those born with FASD, the WA FASDPN clinics have confirmed early diagnosis and a nurturing home environment significantly reduces disability and lifetime costs (Astley, 2010).

FASD Facts

- FAS was discovered in 1968 (Ulleland, 1972). Washington State is world renowned for this discovery.
- An estimated 870 children are born with FASD in Washington State each year (1% of all births).
  An estimated 70,000 individuals with FASD of all ages currently live in Washington State. (SAMHSA, 2006)
- FASD is 100% preventable. Washington State has published empirical evidence confirming its FASD prevention efforts are working. (Astley, 2004)
- FASD is the leading known cause of intellectual disabilities. (Stratton, 1996).
- FASD is not just a health care issue. Its primary impact is on schools, foster and adoption services, the justice system, and mental health services.
- Less than 10% of adults with FASD live independently or remain employed (Streissguth, Barr, Kogan, & Bookstein, 1996).
- An early accurate diagnosis, intervention, and a nurturing home environment are 3 factors empirically confirmed to substantially improve brain function and lifetime achievement among individuals with FASD (Astley, 2010; Streissguth, Barr, Kogan, & Bookstein, 1996).

What has Washington State Achieved to Date Regarding Evidence-Based and Best Practices for FASD Screening, Diagnosis, Prevention, Intervention, and Policy?

➢ EVIDENCE-BASED PRACTICES FOR EARLY SCREENING AND DIAGNOSIS OF FASD

1. **The Washington State FAS Diagnostic & Prevention Network** (fasdpn.org) is a network of interdisciplinary community-owned FASD diagnostic clinics led by the core clinical/research/training clinic at the University of Washington. The University of Washington clinic conducts 90% of the FASDPN diagnostic evaluations. The Network clinics conduct 10% of the FASDPN diagnostic evaluations. The FASDPN has been funded by the WA General Fund since 1995.

   The FASDPN was established in 1995 through enactment of RCW 70.96A.500 (Fetal Alcohol Screening and Assessment Services) **(Appendix D)**.

   > "Findings—Purpose—1995 c 54: *The legislature finds that fetal alcohol exposure is among the leading known causes of mental retardation in the children of our state. The legislature further finds that individuals with undiagnosed fetal alcohol exposure suffer substantially from secondary disabilities such as child abuse and neglect, separation from families, multiple foster placements, depression, aggression, school failure, juvenile detention, and job instability. These secondary disabilities come at a high cost to the individuals, their family, and society. The legislature finds that these problems can be reduced substantially by early diagnosis and receipt of appropriate, effective intervention*."

   The accomplishments of the FASDPN to date are described in full on its website (fasdpn.org) and briefly summarized below:

   A. **The FASDPN has provided 100% of the interdisciplinary FASD diagnostic and treatment evaluations in Washington State for the past 20 years**. The FASDPN was the first to introduce the highly effective and cost efficient interdisciplinary approach to FASD diagnosis.(Clarren & Astley, 1998; Astley, 2010). It was also the first to introduce an evidence-based FASD diagnostic system (the FASD 4-Digit Code(Astley, 2013). This FASD diagnostic model is now recognized as clinical best practice (SAMHSA, 2014) and replicated internationally.

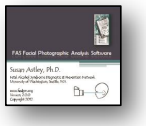
      Twenty years of FASDPN patient surveys (Astley, 2014) document:

      - 98% of families report receiving information not available to them elsewhere.
      - 89% report the diagnosis afforded them access to interventions that met their needs.
      - 100% report they would recommend the service to others.

In the words of one caregiver of a 10-year old child who received a FASD diagnosis ""*I cannot say enough good things about your services. A proper diagnosis has resulted in: change of school placement, OT/PT services provided by the school district, a referral to mental health in hopes of finding a therapist w/background in neurodevelopmental problems and patient's psychiatrist reducing his medications.*"

B. **The FASDPN provides 100% of the FAS screening and surveillance in Washington State**.

Through translational research (the rapid translation of research into clinical practice) the FASDPN created an evidence-based FAS screening tool (Astley et al., 1996, 2002) by first identifying the unique facial features of FAS and then creating FAS facial recognition software to identify these facial features from a digital photograph (Astley, 2014a). This software is now used worldwide.



The FASDPN used this facial recognition software to screen all children entering the King County Foster Care Passport Program over a 10 year period for FAS. This required nothing more than a digital facial photograph and a 5 minute computerized analysis. All children who screened positive for the FAS facial features received a full FASD diagnostic evaluation. Over 95% of the screen-positives received a diagnosis of FAS. This screening led to the discovery that one out of every 100 foster children in foster care has FAS (10 times higher than in the general population) (Astley et al., 2002).

This FAS screening program also led to the discovery that the prevalence of FAS births in Washington State decreased significantly in the same years maternal drinking during pregnancy in Washington State decreased significantly. (Astley, 2004)

The FASDPN currently provides FAS photo screening for Child Health & Education Tracking (CHET) and the Foster Care Assessment Program (FCAP).

C. **The UW FASDPN provides FASD training to hundreds of Washington State healthcare, educational, correctional, and social service providers annually**.

Training opportunities include:

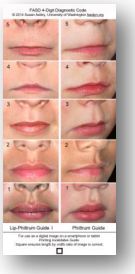
- The 1-Day Observation Training: Community professionals learn how to coordinate their efforts with the services of the FASDPN clinics to best serve individuals with FASD. These community professionals from healthcare, education, corrections, and social service are the professionals the FASDPN relies on to identify and refer individuals to the FASD clinics. They are also the professionals the FASDPN clinic will refer the patient back to for ongoing intervention services. By directly observing the FASDPN diagnostic team conduct two FASD diagnostic evaluations, their community role in this process

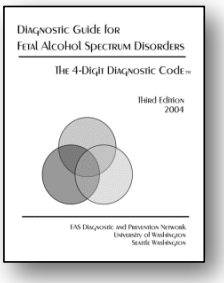
becomes crystal clear. Over 10,000 Washington State professionals have been trained to date. Training evaluations are sent monthly to the State. 100% have rated the training good to excellent.

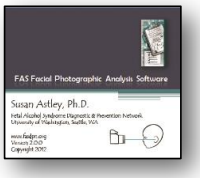
In the words of one community professional who attended the training: "*To the inspiring FASD team members: Thank you so much for allowing me to observe your evaluations. What a treat to be able to watch in awe as each and every one of you evaluated and gained support with both child and mom with such grace and expertise. From the clinic coordinator's initial communication, to the incredible training, the lightning fast pace at which you produce those reports, the humility in delivering the diagnostic news, etc., etc.; from one outside agency, I will be happy to refer kids here (as we have in the past) and feel honored to be able to share my first-hand experience of the process! Thanks for the opportunity.*"

- Diagnostic Team Training: The UW FASDPN clinic provides diagnostic teams with instruction on how to establish an interdisciplinary FASD diagnostic clinic using the FASD 4-Digit Code. Over 150 teams have been trained worldwide including 6 in Washington State.
- FASD 4-Digit Code Online Course: The UW FASDPN clinic provides accredited online instruction for how to use the FASD 4-Digit Diagnostic Code. Over 700 professionals worldwide have completed the course. On a scale of 1 to 5, with 5 being excellent, the average score for the Online Course is 4.9.

D. **The UW FASDPN has developed the largest FASD clinical/research database and conducts translational research that has led to the development of FASD screening, surveillance, diagnostic, and intervention programs and tools used worldwide**.







Publications resulting from this research are posted on fasdpn.org.

➢ EVIDENCE-BASED PRACTICES FOR FASD PREVENTION

1. The **Parent-Child Assistance Program (PCAP)** (http://depts.washington.edu/pcapuw/) has been funded through Washington State DSHS Division of Behavioral Health and Recovery (DBHR) since 1997 by a combination of Federal Medicaid and State General Funds. PCAP:
   A. Enrolls women in Washington State who are at highest risk for delivering children with FASD: those who have an alcohol abuse problem, or who have already delivered a child with FASD.
   B. Provides intensive case management intervention to nearly 900 women and their families in eleven Washington State counties.
   C. Demonstrates consistently positive research outcomes and publishes findings in peer-reviewed journals (http://depts.washington.edu/pcapuw/).
   D. Demonstrates significant cost savings for Washington State (Casey Family Programs & Grant, 2013).
   E. Has been identified as an evidence-based practice by federal programs and clearinghouses, including the Association of Maternal and Child Health Programs (2012), the California Evidence-Based Clearinghouse for Child Welfare (2010,2013), and the Office of Juvenile Justice and Delinquency Prevention Model Program (2005, 2010).
   F. Maintains quality control and project fidelity via consistent statewide training and evaluation.
   G. Conducts research that has led to the development of screening and treatment modifications for adults with FASD that are being tested and adopted worldwide (Grant, Brown, Graham et al., 2013).
   H. Utilizes its statewide database to examine questions relevant to state child welfare policy and practices. For example, recurrent childbearing among substance-abusing mothers is a serious concern nationwide. PCAP clinical observations indicated that mothers whose children were removed from their custody often reacted by having a "replacement" baby. PCAP examined repeat alcohol/drug-exposed births among 795 clients. Consistent with our hypothesis we found that among women whose most recently delivered child had been removed from their care, the odds of having a subsequent birth increased *nearly two-fold* and the odds of having a subsequent *exposed* birth *increased three-fold*. The published paper discusses child welfare policy and practice implications and offers recommendations (Grant, Graham, Ernst et al., 2014).
   I. Utilizes its statewide database to collaborate with researchers at WSU in studying questions related to maternal substance abuse (e.g. rural/urban differences in substance abuse and mental health treatment services and outcomes; effects of contingency management on tobacco cessation recidivism.
   J. Trains and consults on the PCAP model throughout the world. In 2009 the Government of Alberta Institute of Health Economics recommended that Canada encourage programs based on the PCAP model (Institute of Health Economics, 2009). PCAP has now been replicated at forty Canadian sites with funding from provincial governments.

Mothers enrolled in PCAP are some of the highest risk women in Washington State, and they exemplify the intergenerational nature of familial substance abuse and dysfunction. *They were themselves the neglected and abused children in our communities just a decade or two ago* (Grant, Huggins, Graham et al., 2011). As children, over 90% had substance abusing parents, 63% were physically and/or sexually abused, 64% ran away from home, 30% had child welfare services involvement, and over half did not graduate from high school. As young mothers, they are likely to give their babies the same kind of upbringing they experienced as children unless we reach out with care, engagement, and intervention.

All PCAP clients have substance abuse disorders. Most are on Medicaid and have publicly funded core services available to them, but they do not tend to access these services or succeed on their own. For example, before enrollment in PCAP, 34% did not have a regular healthcare provider and 88% were not using a family planning method; 86% had previously been in inpatient or outpatient treatment (an average of three times); 43% were homeless or transient. The PCAP model, based on relational theory and motivational interviewing concepts, *offers outreach and engagement* to clients from trained, supervised case managers who provide support, structured goal setting, and consistent coaching (Grant, Ernst, & Streissguth, 1999). PCAP case managers are realistic role models who inspire hope—many are in long-term recovery and have overcome difficult life circumstances similar to those experienced by clients.

The PCAP approach makes a difference to clients:

- *"There were times when I felt like I was going to relapse and my case manager would be there for me, and she'd keep checking on me and I'd get through it. I've learned so much about myself and being responsible again and being a good mother. It was all what she taught me—she changed my life for me."*
- *"She helped me establish goals; she's helped me achieve my goals. She's taught me responsibility, dependability. After three years of working with her, I see myself as a strong, independent woman."*
- *"Before PCAP I never thought about goals. They showed me the right direction. They showed me that I am responsible. That no matter who I am or what I do, I am somebody. It is never too late."*

➢ EVIDENCE-BASED AND BEST PRACTICES FOR FASD INTERVENTION

1. **The Substance Abuse and Mental Health Services Administration (SAMHSA)** most recent Treatment Improvement Protocol (TIP) #58 is entitled "Addressing Fetal Alcohol Spectrum Disorders" (SAMHSA, 2014). Members of the University of Washington FADU and FASDPN programs, as well as members of the IAWG were coauthors of this document. FASD programs developed in Washington State are referenced throughout the TIP. It offers best-practices guidelines based on an evidence base of scientific research findings and clinical practice theory and principles. The TIP provides: 1) appropriate counseling methods for behavioral health practitioners; 2) support for program administrators to implement recommendations; and 3) an in-depth literature review.

2. **NOFAS WA** (nofaswa.org). Substitute Senate Bill 5688 also stipulated "*The interagency agreement shall provide a process for community advocacy groups to participate in the review and development of identification, prevention, and intervention programs administered or contracted for by the agencies executing this agreement*." NOFAS WA is a nonprofit 501(C) (3) family advocacy program established in 2003. NOFAS WA is an alliance of families and professionals supporting individuals with FASD, the families that care for them, and the systems that serve them. It hosts programs like FASt Friends, Teen Group, Family Camp, Trainings, and Conferences to empower families to succeed. NOFAS WA is an affiliate of the National Organization of Fetal Alcohol Syndrome. NOFAS Washington State received periodic funding support from the State prior to 2008 for targeted activities like Family Camp.

3. **Families Moving Forward with FASD** (http://depts.washington.edu/fmffasd/). Intervention services guided by clinicians with expertise/experience in FASD best meet the needs of families. Evidence-based programs like the University of Washington Families Moving Forward (FMF) with FASD provide this clinician training and parent support (Bertrand, 2009).

4. **Families confirm access to effective intervention starts with an accurate FASD diagnosis**. Twenty years of patient surveys confirm the FASDPN's interdisciplinary approach to diagnosis using the 4-Digit Code afforded them substantial access to community-based interventions that met their needs (Astley, 2014). For a patient to derive the greatest benefit from their FASD diagnostic evaluation, they need an interdisciplinary team that can: 1) render an accurate diagnosis under the umbrella of FASD; 2) generate a comprehensive intervention plan tailored to their specific needs and circumstances; and 3) present all of this in a comprehensive medical summary report that effectively informs and educates the family and their community service providers. In one 4-hour FASD evaluation, the patient is evaluated by a pediatrician, psychologist, speech language pathologist, and occupational therapist. Patients reported this single 4-hour assessment provided them with more information and access to

services than the multitude of uncoordinated services the families reported accessing prior to coming to the FASDPN clinic.

5. **UW Fetal Alcohol and Drug Unit researchers have developed practices effective with people who have FASD and published these in peer-reviewed papers**:
   - In 1992-1996 the Centers for Disease Control and Prevention (CDC) funded Dr. Ann Streissguth to study the occurrence and range of adverse effects of FASD across the lifespan. The study documented risk and protective factors among 451 individuals diagnosed with an FASD (age range 6 to 51 years).

     The Final report and the 2004 published paper continue to be cited worldwide as the most definitive sources of information on this topic. (Streissguth et al., 1996, 2004)

   - People with FASD are at high risk for substance abuse problems. Using the PCAP database, UW researchers conducted the first study of substance abuse treatment participation among people with FASD compared to those without FASD (Grant, Brown, Graham & Ernst, 2014). Findings: women with FASD were less likely to attend and complete inpatient and outpatient treatment; those with FASD were more likely to complete treatment within a residential versus outpatient setting. Detailed recommendations were developed for treatment accommodations to address impairments in FASD (Grant, Brown, Dubovsky, & Ries, 2013).
   - UW researchers developed and tested a 27-item Life History Screen interview protocol (LHS) to screen individuals at treatment intake for characteristics typically found in FASD in order to inform assessments and treatment planning (Grant, Brown, Graham, et al., 2013). Findings: the LHS shows promise as an efficient self-report screen for identifying possible FASD. Researchers in Canada and Germany are now conducting government-funded studies to further develop psychometric properties of the LHS.
   - People with FASD have 5 times greater risk for suicide attempt than those in the general population. UW researchers described clinical profiles of a sample of people with FASD, identified suicide risk and protective factors, and made recommendations for reducing suicide attempt among people with FASD (Huggins et al., 2008).
   - People with FASD are at high risk for criminal justice system involvement. UW researchers have developed detailed strategies for assessing prenatal alcohol exposure in legal settings (Brown et al., accepted).
   - Early intervention can reduce the likelihood that people with FASD will have adverse lifelong effects. UW researchers described how neonatal cranial ultrasound results led to an early FAS diagnosis and successful intervention in an infant whose mother was enrolled in PCAP (Grant, Bookstein, Whitney, & Streissguth, 2006).
   - UW researchers described the neuropsychological assessments administered to PCAP clients who have FASD, and illustrated how results have been used to help multidisciplinary teams respond effectively to affected individuals (Sparrow et al., 2013).

➢ POLICIES THAT IMPROVED FASD IDENTIFICATION, PREVENTION, AND INTERVENTION.

1. Washington State was the first to discover FAS in 1968. In 1973 the University of Washington introduced the term FAS into the medical literature. These actions paved the way for the following national public health policies:

   A. In 1981, The FDA posted the first **Surgeon General's Advisory on Alcohol and Pregnancy**: "*According to the Surgeon General, Women should not drink alcoholic beverages during pregnancy because of the risk of birth defects*".

   B. In 1988 the **Alcohol Beverage Labeling Act** was enacted. "*Government Warning: (1) According to the surgeon general, women should not drink alcoholic beverages during pregnancy because of the risk of birth defects. (2) Consumption of alcoholic beverages impairs our ability to drive a car or operate heavy machinery, and may cause health problems.*"

2. In 1992, Washington State was the first state to establish the position of "**FAS State Coordinator**". In 2003, SAMHSA expanded this to the National Association of FASD State Coordinators (SAMHSA 2003, 2014).

3. In 1992, the University of Washington opened the **first interdisciplinary FASD diagnostic clinic** (Clarren & Astley, 1998). In 1997 the UW went on create the **first case-defined FASD diagnostic system** (the FASD 4-Digit Diagnostic Code) (Astley & Clarren, 1997). This interdisciplinary approach to FASD diagnosis using rigorous case-defined guidelines is now regarded as clinical best practice worldwide (SAMHSA, 2014).

4. In 1993, Washington State enacted RCW 66.16.110 **Birth Defects from Alcohol-Warning Signs**. *The board shall cause to be posted in conspicuous places, in a number determined by the board, within each state liquor store, notices in print not less than one inch high warning persons that consumption of alcohol shortly before conception or during pregnancy may cause birth defects, including fetal alcohol syndrome and fetal alcohol effects*.

5. In 1995 Washington State was the **first to establish a statewide network of clinics** (the WA FAS Diagnostic & Prevention Network) through Senate Bill 5688. This Senate Bill served as the template for legislatures nationwide to establish statewide FASD diagnostic networks.

6. **The FASD Interagency Work Group** (fasdwa.org). In 1995, the FASD-IAWG was established through Senate Bill 5688 to ensure coordination of DSHS, DOH, DOC, OSPI, and UW programs for individuals impacted by FASD and women at risk of bearing children with FASD. In 2004 the IAWG composed and posted on its website a comprehensive historical record of all programs and policies related to FASD implemented in Washington State.

7. In 1998, Washington State enacted RCW 13.34.805: **Drug-Affected and Alcohol-Affected Infants – Comprehensive Plan**. *The Department of Health and the Department of Social and*

Health Services shall develop a comprehensive plan for providing services to mother who (a) have delivered a drug or alcohol exposed or affected infant, and (b) meet the definition of at-risk eligible persons in RCW 74.09.790 and who have a child up to three years of age. The services to be provided by the plan will include those defined in RCW 74.09.790. The plan shall provide for the coordination of services through community-based programs and among: (i) The department; (ii) the departments' divisions; and (iii) other state agencies. The plan shall include recommendations to the legislature for implementing the plan and any alternative methods for addressing the needs of these mothers and their children

8. In 2004, Governor Locke proclaimed September 9th as" **FASD Awareness Day"**. First recognized in 1999, International FASD Awareness Day helps raise awareness about the range of conditions that can result from alcohol use during pregnancy. September 9, 2004 was enacted as National FASD Day by the 108th congress of the U.S.

CURRENT CHALLENGES AND RECOMMENDED SOLUTIONS

Washington State is the leader in the field of FASD, being the first to discover FASD, and the first to develop evidence-based tools and programs for the screening, diagnosis, intervention, and prevention of FASD. Although Washington State's prevention efforts are working, the State's capacity to screen, diagnose, treat, and prevent FASD falls far below the statewide need/demand for such services. Our recommendations below focus primarily on increasing the capacity of our evidence-based screening, diagnosis, intervention, and prevention efforts.

A. Screening and Diagnosis of FASD

1. **Challenge**: Washington State's FASD diagnostic capacity does not meet diagnostic demand. An estimated 870 children with FASD are born each year in Washington State. At 2014 funding levels, the WA FASDPN is funded to conduct only 110 diagnostic evaluations per year. The average wait time for a family seeking a FASD diagnostic evaluation is 9 months. For children birth to three years of age, this translates into lost opportunities for early intervention.

   Solution: Maintain current FASD diagnostic capacity at the core University of Washington FASDPN Clinic, and if possible increase FASD diagnostic capacity through the FASDPN Network Clinics. Doubling statewide capacity would reduce average wait time to 4.5 months.

   Cost: A FASD diagnostic evaluation at the FASDPN costs $2,900. Doubling diagnostic capacity would cost $319,000 (110 x $2,900).

   Cost Savings: *Each $2,900 evaluation conducted by the FASD saves $4,900 in ineffective diagnostic evaluations*. Twenty years of patient records confirm that patients with prenatal alcohol exposure seek out an FASD evaluation by any means possible (Astley, 2014). A 4-hour interdisciplinary FASD diagnostic evaluation conducted by a pediatrician, psychologist, speech language pathologist, occupational therapist,

social worker and family advocate at the FASDPN costs $2,900. The cost of this evaluation (4 hours with an interdisciplinary, and 3-days effort by the clinic coordinator who schedules the appointment, collects all historical records (birth, school, medical, placement) that contain vital information required to derive the FASD diagnosis, and constructs the 12-page template medical summary report) is $2,900. A family seeking a diagnosis by scheduling four separate, uncoordinated evaluations with these same clinicians would cost over $7,800. The former results in an accurate FASD diagnosis and effective intervention plan. The latter does not. This interdisciplinary approach of FASD diagnosis is recognized as best practice nationwide (SAMHSA, 2014). An early accurate FASD diagnosis reduces the lifetime cost of an individual's FASD disability by hundreds of thousands of dollars (Olson et al., 2007; Astley, 2010). The benefit (HeraldNet, 12/24/14) to the individual and their family is immeasurable.

2. **Challenge**: A comprehensive neuropsychological assessment is an important component of a FASD diagnostic evaluation and is essential to informing effective treatment and service delivery. Children and adolescents referred to the FASD diagnostic clinics often have these assessments conducted by the schools and shared with the clinics. The FASD clinics collect these existing records to reduce the time and cost of the FASD evaluation. Adults referred to the clinics rarely have this data in their records. Most adults seeking an FASD diagnostic evaluation are on Medicaid and most neuropsychologists do not accept Medicaid payment. Therefore most adults seeking an FASD diagnostic evaluation do not have affordable access to adult neuropsychological evaluation services. This can prevent them from receiving a FASD diagnostic evaluation.

   Solution: Increase capacity for neuropsychological assessment of adults on Medicaid.

   Cost of Medicaid reimbursement: approximately $720 per neuropsychological assessment. Actual cost per assessment: approximately $1,700 to $2,500, often not fully covered by insurance.

3. **Challenge**: Programs working with at-risk children are not screening effectively for prenatal alcohol exposure. Clinicians are more likely to screen for illicit drug use during pregnancy than alcohol use, even though alcohol is more harmful to the developing fetus.

   Solution: Educate clinicians statewide on the importance of screening for and documenting prenatal alcohol exposure. Documentation of prenatal alcohol exposure serves to identify at-risk children that require close developmental monitoring. The 1-Day Training at the UW FASDPN clinic provides this training.

   Cost: Doubling diagnostic capacity doubles the number of 1-Day Training sessions available at no additional cost. The training sessions at the UW FASDPN take place

during each FASD diagnostic evaluation and are conducted by the team already assembled to conduct the diagnostic evaluation.

B. Prevention of FASD

1. **Challenge**: The State First Steps Database (2010) identified at least 2,606 alcohol and drug-abusing pregnant or postpartum women (PPW) with Medicaid births. PCAP has the capacity to serve approximately 900 (35%) of these women. Approximately 1,700 women who are eligible for PCAP are not being served. Most PCAP sites have waiting lists.

   Solution: Maintain current PCAP funding in eleven counties and if possible expand PCAP to additional counties that have high rates of prenatal substance abuse, such as Thurston.

   PCAP Cost: Approximately $5200 per client per year including direct services to families, and training and evaluation by the University of Washington. The cost of a full site serving approximately 100 women (e.g. in Thurston County) is $520,000 per year. It is not reasonable or cost effective to operate PCAP in remote counties where need is low, but statewide cost to serve even half of the eligible women not being served (approximately 850) is $4.42 million per year.

   Cost Savings (Casey Family Programs & Grant, 2013):

   - *Fewer substance exposed births*. At exit from PCAP, 79% of moms are no longer at risk for delivering another alcohol/drug affected infant because they are in successful recovery or are using family planning on a regular basis. The estimated total lifetime cost for every infant born with Fetal Alcohol Syndrome (FAS) is $2 million. **PCAP data show over $20 million in lifetime cost savings** because of effective intervention among the PCAP mothers who were former binge drinkers.
   - *Reduced dependence on child welfare*. Children of mothers in PCAP who were in out-of-home care and reunified at PCAP exit had a shorter length-of-stay (3.8 months), on average, than Washington's statewide average (20.4 months). For each successful reunification, **savings of over $21,000 per child can be realized**.
   - *Reduced dependence on public assistance.* From 2007 to 2012, Temporary Assistance for Needy Families (TANF) was the main source of income for 61% of women entering PCAP compared to only 31% at exit.
   - *Increased employment.* From 2007 to 2012, employment was the main source of income for 3% percent of women entering PCAP, compared to 27% at exit, resulting in greater tax revenue from increased earnings.

2. **Challenge**: Women with alcohol abuse disorders need high-quality treatment, and those with more severe substance abuse or cognitive problems need residential treatment. In Washington State there are only 156 state-funded PPW residential treatment beds, with only 130 slots for childcare.

Solution: Increase PPW residential and outpatient substance abuse treatment capacity across the state.

Cost: In 2013 the average cost was $7,545 per client for residential treatment services and $1,274 per client for outpatient treatment.

Cost Savings Increasingly strong evidence finds that treatment pays for itself (Center for Substance Abuse Treatment, 2002). Every $1 invested yields a return of between $4 and $7 in reduced drug-related crime, criminal justice costs, and theft. Savings can exceed costs by 12 to 1 when health care savings are included. Among pregnant women who are treated, newborns weigh more, have greater gestational age, are less likely to require care in the neonatal intensive care unit (NICU), and have shorter NICU stays if admitted. Residential and combined residential-outpatient treatment appear to be the most cost effective treatment modalities

3. **Challenge**: FASDs are preventable, and health care providers are in an ideal position to screen women for alcohol use and risk for becoming pregnant. Most health care providers do not discuss FASD prevention with women.

   Solution: The Washington State Department of Health has developed comprehensive recommendations and guidelines, entitled "Substance Abuse During Pregnancy: Guidelines for Screening and Management" (WA DOH, 2013). These guidelines need to be more widely distributed to healthcare providers throughout the state via no-cost websites and list serves.

   Cost: The Guidelines can be promoted and distributed throughout the state at little cost via current health care and substance abuse websites and list serves.

Interventions for Individuals with FASD

1. **Challenge**: Families are the primary support structure for children and adults in Washington State living with FASD. Family advocacy is vital for supporting these families. NOFAS WA hosts programs like FASt Friends, Teen Group, Family Camp, Trainings, and Conferences to empower families to succeed. NOFAS WA is a nonprofit that struggles to keep its programs open.

   Solution: Reinstate funding support for community advocacy groups like NOFAS WA.

   In 1995, Senate Bill 5688 stipulated the participation of community advocacy groups. DSHS provided $100,000/year support for community advocacy programs between 1995 and 2008. Families would benefit greatly if this support was reinstated.

2. **Challenge**: Intervention services guided by clinicians with expertise/experience in FASD best meet the needs of families. Evidence-based programs like Families Moving Forward (FMF) with FASD provide this clinician training and parent support. The current capacity of programs like FMF is too low to meet statewide demand.

   Solution: Increase the capacity of programs like FMF.

D. Policy Changes to Improve FASD Identification, Prevention, and Intervention

1. **Challenge**: FASD diagnostic and prevention efforts in Washington State are limited by their heavy reliance on State General Funds. More specifically:

   A. FASD diagnostic capacity through the FASDPN clinics is limited in Washington State because over 70% of patients seeking a diagnostic evaluation are on Medicaid (Astley, 2010) and Medicaid and/or private insurance alone covers less than one third of the cost of a diagnosis. This is not unique to Washington State. In a formal study conducted by the University of Alaska Anchorage in 2004 (BHRS, 2004), the average cost of conducting a FASD diagnosis in the State of Alaska using the University of Washington interdisciplinary model was $4,821. Only $1,076 could be billed to and collected from Medicaid and/or private insurance. Recognizing that Medicaid and/or insurance alone did not cover the full cost of a diagnosis, Alaska established a Provider Agreement payment of $3,000 per FASD diagnosis to assist interdisciplinary teams in recovering the cost of a diagnosis in their community (State of Alaska, 2012). Washington State established a similar provider agreement in 2007. The cost of a FASD evaluation in Washington State is approximately $2,900. The WA FASDPN clinics receive $2,000 per evaluation from State General Funds to offset what cannot be reimbursed through Medicaid and/or private insurance.

   B. FASD prevention efforts through PCAP have been funded through WA DSHS Division of Behavioral Health and Recovery (DBHR) since 1997 by a combination of Federal Medicaid and State General Funds.

      Solution: Explore all available opportunities to diversify funding sources, including maximizing federal Medicaid funding in order to reduce the fiscal impact on state general funds. **Update:** Discussions are currently underway with members of IAWG and key State Agency personnel to address this issue.

2. **Challenge**: Many patients with FASD are unable to access existing effective interventions recommended by the FASDPN clinics. These interventions include services for cognitive, behavioral, language, and motor sensory impairments. Qualifying for services through the DDA (Developmental Disability Administration) can be an important first step in obtaining services and supports.

Solution: Revise DDA eligibility criteria so that applicants with FASD, not just those with FAS, can be considered for eligibility under "*another neurological or other condition*. **Update**: Members of the IAWG have been working effectually for the past six months to formulate these revisions. We are pleased to report the revisions are near completion with a projected implementation date of early 2015, pending approval.

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Appendices

A. House Bill 2737 (2014)

B. Substitute Senate Bill 5688 (1995)

C. FASD Interagency Work Group Members (2014)

D. RCW 70.96A.500 Fetal Alcohol Screening and Assessment Services (1995)

APPENDIX A

H-3637.2

HOUSE BILL 2737

State of Washington 63rd Legislature 2014 Regular Session

By Representatives Kagi, Sawyer, Smith, Ryu, Gregerson, Goodman, and Freeman

Read first time 01/29/14. Referred to Committee on Early Learning & Human Services.

AN ACT Relating to fetal alcohol exposure; amending RCW 70.96A.510; adding new sections to chapter 66.28 RCW; and creating a new section.

BE IT ENACTED BY THE LEGISLATURE OF THE STATE OF WASHINGTON:

NEW SECTION. **Sec. 1.** (1) The legislature finds that fetal alcohol exposure can cause serious mental and physical disorders and disabilities in children. These disorders are preventable if a mother does not drink during pregnancy. With the advent of private alcohol retailers, there is now increased access to alcohol. The legislature intends to require signage warning women about the dangers of fetal alcohol exposure in all stores selling alcohol.

(2) The legislature further finds that by collecting evidence-based practices around the identification, prevention, and interventions for fetal alcohol spectrum disorders, the number of affected individuals can decrease and those who are affected can improve their lives. Finally, by convening a work group of stakeholders, the legislature can become better informed about steps that can be taken to appropriately address fetal alcohol exposure.

NEW SECTION. **Sec. 2.** A new section is added to chapter 66.28 RCW to read as follows:

(1) At a minimum, premises that serve alcohol for on-premises consumption, grocery store licensees, beer and wine specialty shop licensees, breweries, wineries, and taverns shall post in a conspicuous place easily seen by patrons a printed sign at least eighteen inches by twenty-four inches in size, with letters at least two inches high, warning that consumption of alcohol during pregnancy can cause birth defects.

(2) This section does not apply to self-service minibars in hotel guest rooms.

NEW SECTION. **Sec. 3.** A new section is added to chapter 66.28 RCW to read as follows:

The board shall have the authority to adopt rules to carry out section 2 of this act in a manner that will increase the visibility of signage. The contents of section 2 of this act provide the minimum requirements regarding warning that consumption of alcohol during pregnancy can cause birth defects, but the board may adopt additional rules beyond those minimum requirements to ensure that customers observe these warnings.

Sec. 4. RCW 70.96A.510 and 1995 c 54 s 3 are each amended to read as follows:

(1) The department of social and health services, the department of health, the department of corrections, and the office of the superintendent of public instruction shall execute an interagency agreement to ensure the coordination of identification, prevention, and intervention programs for ((~~children)~~) individuals who have fetal alcohol exposure, and for women who are at high risk of having children with fetal alcohol exposure.

The interagency agreement shall provide a process for community advocacy groups to participate in the review and development of identification, prevention, and intervention programs administered or contracted for by the agencies executing this agreement.

(2) The interagency agreement shall provide for a work group cochaired by the department of social and health services, the University of Washington fetal alcohol syndrome diagnostic and

prevention network, and the University of Washington fetal alcohol and drug unit to address fetal alcohol exposure issues related to identification, prevention, and intervention. This work group shall include the department of health, the department of corrections, the office of the superintendent of public instruction, and other interested organizations identified by the department of social and health services, the University of Washington fetal alcohol syndrome diagnostic and prevention network, and the University of Washington fetal alcohol and drug unit.

(3) By December 1, 2014, the work group shall develop recommendations and provide a report to the appropriate committees of the legislature relating to:

(a) Identification of evidence-based practices for early screening and diagnosis of fetal alcohol spectrum disorders;

(b) Identification of evidence-based practices for prevention of fetal alcohol spectrum disorders;

(c) Identification of evidence-based practices for interventions that can be used with individuals experiencing fetal alcohol spectrum disorders; and

(d) Recommendations of policy changes that would improve the identification, prevention, or interventions related to fetal alcohol spectrum disorders.

--- END ---

APPENDIX B

CERTIFICATION OF ENROLLMENT

SUBSTITUTE SENATE BILL 5688

Chapter 54, Laws of 1995

54th Legislature
1995 Regular Session

Fetal alcohol exposure prevention

EFFECTIVE DATE: 7/23/95

Passed by the Senate March 13, 1995
YEAS 48 NAYS 0

JOEL PRITCHARD
President of the Senate

Passed by the House April 5, 1995
YEAS 95 NAYS 0

CLYDE BALLARD
Speaker of the House of Representatives

Approved April 17, 1995

MIKE LOWRY
Governor of the State of Washington

CERTIFICATE

I, Marty Brown, Secretary of the Senate of the State of Washington, do hereby certify that the attached is **SUBSTITUTE SENATE BILL 5688** as passed by the Senate and the House of Representative on the dates hereon set forth.

MARTY BROWN
Secretary

FILED

April 17, 1995 – 3:45 p.m.

Secretary of State
State of Washington

SUBSTITUTE SENATE BILL 5688

Passed Legislature - 1995 Regular Session

State of Washington **54th Legislature** **1995 Regular Session**

By Senate Committee on Human Services and Corrections (originally sponsored by Senators Hargrove, Long, Franklin, Rasmussen, C. Anderson, Kohl, Prentice, McAuliffe, Fairley, Drew, Smith, Heavey, Sheldon, Wojahn, Bauer and Winsley)

Read first time 03/01/95.

AN ACT Relating to fetal alcohol exposure; adding new sections to chapter 70.96A RCW; and crating new sections.

BE IT ENACTED BY THE LEGISLATURE OF THE STATE OF WASHINGTON:

NEW SECTION. **Sec. 1.** The legislature finds that fetal alcohol exposure is among the leading known causes of mental retardation in the children of our state. The legislature further finds that individuals with undiagnosed fetal alcohol exposure suffer substantially from secondary disabilities such as child abuse and neglect, separation from families, multiple foster placements, depression, aggression, school failure, juvenile detention, and job instability. These secondary disabilities come at a high cost to the individuals, their family, and society. The legislature finds that these problems can be reduced substantially by early diagnosis and receipt of appropriate, effective intervention.

The purpose of this act is to support current public and private efforts directed at the early identification of and intervention into the problems associated with fetal alcohol exposure through the creation of a fetal alcohol exposure clinical network.

p. 1 SSB 5688.SL

NEW SECTION. **Sec.2.** A new section is added to chapter 70.96A RCW to read as follows:

(1) The department shall contract with the University of Washington fetal alcohol syndrome clinic to provide fetal alcohol exposure screening and assessment services. The University indirect charges shall not exceed ten percent of the total contract amount. The contract shall require the University of Washington fetal alcohol syndrome clinic to provide the following services:

(a) Training for health care staff in community-based fetal alcohol exposure clinics to ensure the accurate diagnosis of individuals with fetal alcohol exposure and the development and implementation of appropriate service referral plans;

(b) Development of written or visual educational materials for the individuals diagnosed with fetal alcohol exposure and their families or caregivers;

(c) Systematic information retrieval from each community clinic to (i) maintain diagnostic accuracy and reliability across all community clinics, (ii) facilitate the development of effective and efficient screening tools for population-based identification of individuals with fetal alcohol exposure, (iii) facilitate identification of the most clinically efficacious and cost-effective educational, social, vocational, and health service interventions for individuals with fetal alcohol exposure;

(d) Based on available funds, establishment of a network of community-based fetal alcohol exposure clinics across the state to meet the demand for fetal alcohol exposure diagnostic and referral services; and

(e) Preparation of an annual report for submission to the department of health, the department of social and health services, the department of corrections, and the office of the superintendent of public instruction which includes the information retrieved under subsection (1) (c) of this section.

(2) The department shall submit to the legislature, by January 1, 1996, a copy of the governor's fetal alcohol syndrome advisory board report.

NEW SECTION. **Sec. 3.** A new section is added to chapter 70.96A RCW to read as follows:

The department of social and health services, the department of health, the department of corrections, and the office of the superintendent of public instruction shall execute an interagency agreement to ensure the coordination of identification, prevention and intervention programs for children who have fetal alcohol exposure, and for women who are at high risk of having children with fetal alcohol exposure.

The interagency agreement shall provide a process for community advocacy groups to participate in the review and development of identification,prevention, and intervention programs administered or contracted for by the agencies executing this agreement.

NEW SECTION. **Sec.4.** If specific funding for the purposes of this act referencing this act by bill number is not provided by June30, 1995, in the omnibus appropriations act, this act is null and void.

Passed the Senate March 13, 1995.
Passed the House April 5, 1995.
Approved by the Governor April 17, 1995.
Filed in Office of Secretary of State April 17, 1995

--- End ---

APPENDIX C

Fetal Alcohol Spectrum Disorder Interagency Work Group (FASD-IAWG)

Members-2014

Name (Alphabetical Order)	Title/Admin
Susan Astley, Ph.D.	Professor of Epidemiology/Pediatrics, University of Washington, Director, WA FAS Diagnostic & Prevention Network (FASDPN) astley@uw.edu
Deanna Bedell, MSW, ACSW	Intake and Substance Abuse Program Manager, DSHS/CA
Jane Beyer	Asst. Sec., DSHS/BHSIA/ADSA
Michelle Bogart	Health Program Manager, CA
Allison Brooks, Ph.D.	Licensed Psychologist, Fetal Alcohol Syndrome Diagnostic and Prevention Network, University of Washington
Heather Carmichael Olson, Ph.D.	Clinical Professor of Psychiatry and Behavioral Sciences, University of Washington, FASDPN, Seattle Children's Hospital Child Psychiatry Outpatient Clinic
Greg Endler	Children's Mental Health Program Administrator, DSHS/BHSIA/MH
Julie Gelo & son Brandan Gelo	Director WA NOFAS, Family Advocate University of Washington FASDPN, WA Alliance for Child Welfare Excellence.
Linda Gil	Program Manager, DDD/DDA
Therese Grant, Ph.D.	Associate Professor of Psychiatry and Behavioral Sciences, University of Washington, Director, Fetal Alcohol and Drug Unit, Associate Director Alcohol & Drug Abuse Institute
Dixie Grunenfelder	Prevention Intervention, Healthy Youth Survey, OSPI
Sherry Guzman	Tulalip Tribes
Carolyn Hartness	Fetal Alcohol Spectrum Disorders Educator/Consultant
Teri Herold-Prayer	Research Manager, DOC
Tracy Jirikowic, Ph.D., OTR/L	Associate Professor of Rehabilitation Medicine, FASDPN, University of Washington
Kay Kelly	Project Director, FASD Legal Issues Resource Center, University of Washington Fetal Alcohol and Drug Unit,
Beth Krehbiel	DDA Intake and Eligibility Program Manager, DSHS-DDA
Jodi Kunkel, BSN, RN	Clinical Nurse Advisor, ADSA/HCS/SUA/Foster Well-Being
Michael Langer	Office Chief – Office of Behavioral Health and Prevention, ADSA/DBHR
Linda Lunsford	Program Manager, DDD/DDA
Chris Osborne	Supervisor, Intake & Eligibility/ Birth-3 Case Manager DSHS-Developmental Disabilities Administration Region 2-Everett/Seattle

Sarah Pine	Behavioral Health Program Manager, FASD Programs and Special Projects, DBHR. Sarah.pine@dshs.wa.gov (360) 725-3807
Sharon Reddick	Quality and Care Management Program Manager, DHS/QCM/HCA
Monica Reeves	Mental Health and Crisis Services Program Manager, DSHS/DDA
Mary Segawa	Alcohol Awareness Program Manager, Director's Office, LCB
Lauri Turkovsky, Ed.D.	Behavioral Health Program Manager, DBHR
Dawn Williams	Program Administrator – Substance Abuse Recovery Unit, DOC
Joan Zerzan, MS RD	Nutrition Consultant, Children with Special Health Care Needs Program, Access, Systems and Coordination Section, Office of Healthy Communities, Division of Prevention and Community Health, DOH

APPENDIX D

RCW 70.96A.500

Fetal alcohol screening and assessment services.

The department shall contract with the University of Washington fetal alcohol syndrome clinic to provide fetal alcohol exposure screening and assessment services. The University indirect charges shall not exceed ten percent of the total contract amount. The contract shall require the University of Washington fetal alcohol syndrome clinic to provide the following services:

(1) Training for health care staff in community-based fetal alcohol exposure clinics to ensure the accurate diagnosis of individuals with fetal alcohol exposure and the development and implementation of appropriate service referral plans;
(2) Development of written or visual educational materials for the individuals diagnosed with fetal alcohol exposure and their families or caregivers;
(3) Systematic information retrieval from each community clinic to (a) maintain diagnostic accuracy and reliability across all community clinics, (b) facilitate the development of effective and efficient screening tools for population-based identification of individuals with fetal alcohol exposure, (c) facilitate identification of the most clinically efficacious and cost-effective educational, social, vocational, and health service interventions for individuals with fetal alcohol exposure;
(4) Based on available funds, establishment of a network of community-based fetal alcohol exposure clinics across the state to meet the demand for fetal alcohol exposure diagnostic and referral services; and
(5) Preparation of an annual report for submission to the department of health, the department of social and health services, the department of corrections, and the office of the superintendent of public instruction which includes the information retrieved under subsection (3) of this section.

[1998 c 245 § 136; 1995 c 54 § 2.]

Notes:

Findings – Purpose – 1995 c 54: "The legislature finds that fetal alcohol exposure is among the leading known causes of mental retardation in the children of our state. The legislature further finds that individuals with undiagnosed fetal alcohol exposure suffer substantially from secondary disabilities such as child abuse and neglect, separation from families, multiple foster placements, depression, aggression, school failure, juvenile detention, and job instability. These secondary disabilities come at a high cost to the individuals, their family, and society. The legislature finds that these problems can be reduced substantially by early diagnosis and receipt of appropriate, effective intervention.

The purpose of this act is to support current public and private efforts directed at the early identification of and intervention into the problems associated with fetal alcohol exposure through the creation of a fetal alcohol exposure clinical network." [1995 c 54 § 1.]

PALPEBRAL FISSURE LENGTH MEASUREMENT: ACCURACY OF THE FAS FACIAL PHOTOGRAPHIC ANALYSIS SOFTWARE AND INACCURACY OF THE RULER

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ABSTRACT

Background
Accurate fetal alcohol spectrum disorder diagnoses require accurate facial measurement. The Fetal Alcohol Syndrome (FAS) Facial Photographic Analysis Software was developed to overcome measurement error known to occur with ruler measurement of the PFL. Recent publications have queried the Software's accuracy.

Objectives
1) Demonstrate the Software's ability to accurately measure a PFL from a 2-dimensional digital facial photograph. 2) Demonstrate the frequency and magnitude of error when the PFL is measured directly by clinicians using a ruler.

Methods
Objective 1: PFLs of mannequins were measured using the Software and a sliding digital caliper, with the latter serving as the gold-standard accurate measure. Mannequins allowed the caliper prongs to be placed directly on the landmarks that define the PFL. Objective 2: PFLs of 1,027 patients evaluated at the University of Washington FAS Diagnostic & Prevention Network were measured with the Software and directly by one or two clinicians using a ruler.

Results
Objective 1: The Software derived PFLs that were identical to or within 0.2 mm of the caliper measures. Objective 2: There was tremendous inter-rater variability in PFLs measured by clinicians using a hand held ruler. Seventy-seven percent of patients had their PFLs measured incorrectly (greater than 1 mm error) by at least one of the two clinicians using a ruler.

Conclusion
The FAS Facial Photographic Analysis Software measures the PFL with the same accuracy as a sliding digital caliper, as it was programmed to do. Direct measurement of the PFL with a ruler is very prone to error.

Key Words: *Fetal alcohol spectrum disorders, palpebral fissure length, FASD 4-Digit Diagnostic Code, WA State Fetal Alcohol Syndrome Diagnostic & Prevention Network*

FAS is a birth defect syndrome caused by maternal use of alcohol during pregnancy. FAS is characterized by growth deficiency, a unique cluster of minor facial anomalies and central nervous system (CNS) structural, neurological and/or functional abnormalities.[1]

The three diagnostic facial features of FAS as defined by the FASD 4-Digit Diagnostic Code[2] are: small palpebral fissure lengths (2 or more standard deviations below the mean), a smooth philtrum (Rank 4 or 5 on the University of Washington Lip-Philtrum Guide), and thin upper lip philtrum (Rank 4 or 5 on the University of Washington Lip-Philtrum Guide).

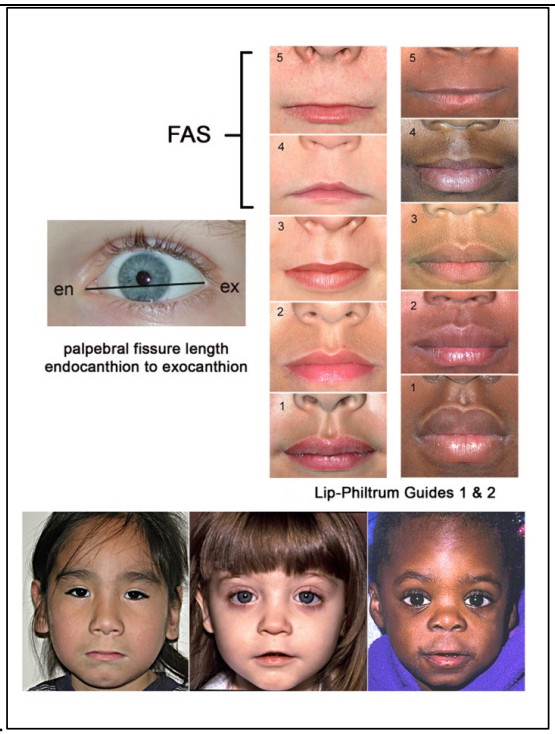


FIG. 1 The three diagnostic facial features of FAS as defined by the FASD 4-Digit Diagnostic Code[2] include: 1) short palpebral fissure lengths (2 or more standard deviations below the mean), 2) A smooth philtrum (Rank 4 or 5 on the Lip-Philtrum Guide), and 3) a thin upper lip (Rank 4 or 5 on the Lip-Philtrum Guide). Lip-Philtrum Guides 1 and 2 are used to rank upper lip thinness and philtrum smoothness. The philtrum is the vertical groove between the nose and upper lip. The guides reflect the full range of lip and philtrum shapes with Rank 3 representing the population mean. Ranks 4 and 5 reflect the thin lip and smooth philtrum that characterize the FAS facial phenotype. Guide 1 is used for Caucasians and all other races with lips like Caucasians. Guide 2 is used for African Americans and all other races with lips as full as African Americans. Examples of the FAS facial phenotype across three races: Native American, Caucasian, and African American.

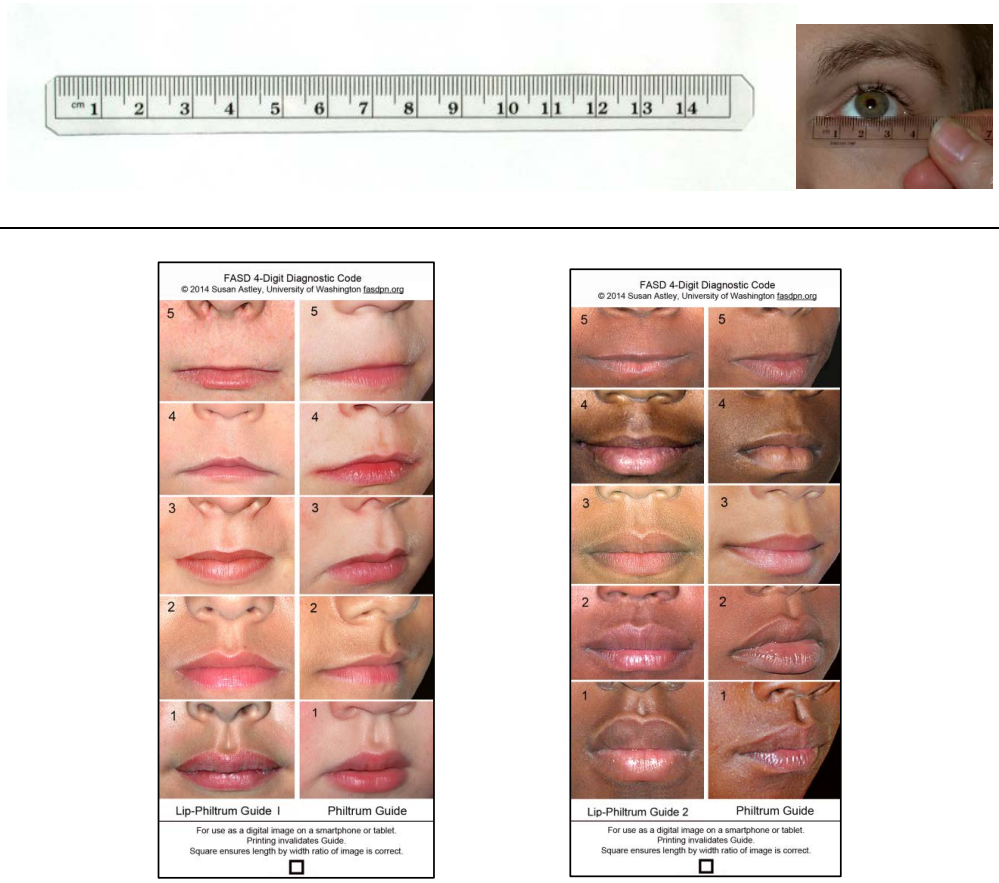


FIG. 2 The University of Washington FAS Diagnostic & Prevention Network (FAS DPN) created Lip-Philtrum Guides 1 and 2 for ranking upper lip thinness and philtrum smoothness and a 15 cm clear plastic ruler with rounded corners for safe measurement of the palpebral fissure.

In 1997, the University of Washington Fetal Alcohol Syndrome Diagnostic & Prevention Network (FAS DPN)[3] developed tools to more accurately measure the facial features of FAS. These tools included Lip-Philtrum Guides 1 and 2 to measure lip thinness and philtrum smoothness and a 15 cm clear plastic ruler with rounded corners to measure the PFL (Figure 2). The Lip-Philtrum Guides improved the accuracy and reproducibility of lip and philtrum measures by introducing pictorial scales that case-defined and rank-ordered lip thinness and philtrum smoothness.[4] The 15 mm clear plastic ruler was an improvement over the foot-long wooden ruler or soft tape measure observed to be used by some clinicians. Despite these improvements, facial

measures were still prone to error. Selecting the correct 5-point rank for lip thinness and philtrum smoothness could prove difficult if the subject's features fell close to the transition between two ranks. And measuring a PFL with a ruler poses many challenges. An accurate measure requires the clinician to place the ruler very close to the open eye and align themselves first with one corner of the patient's eye and then the other corner of the eye to avoid parallax errors. Young patients are often reluctant to allow a clinician to do this and may be unable to sit still enough to allow this measure to be obtained safely and accurately. A 1 mm error in measurement translates into almost 1 SD of error on the PFL growth chart[5], thus there is little room for error. Animations depicting these errors are presented on the FAS DPN website. With the advent of digital photography and computerized image analysis, the University of Washington developed the FAS Facial Photographic Analysis Software in 2003[6] (upgraded in 2012[7]) that allowed the clinician to more accurately measure facial features from 2 dimensional (2D) digital facial photographs (Fig. 3).

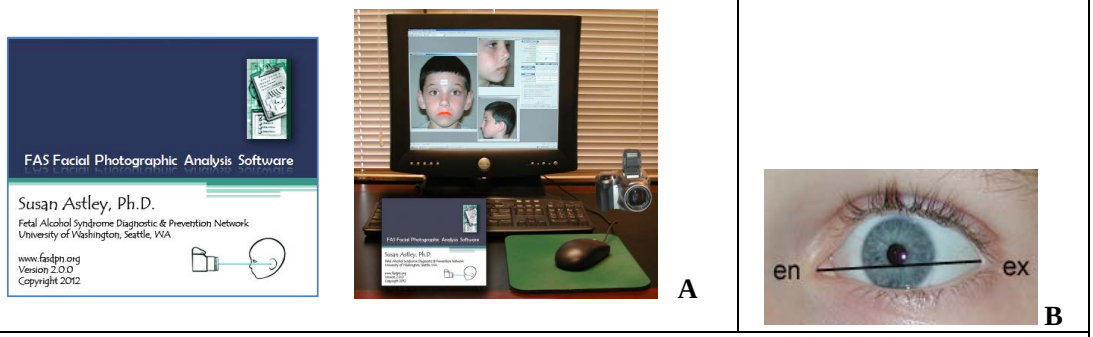


FIG. 3 A) The FAS Facial Photographic Analysis Software[7] allows a clinician to accurately measure the facial features of FAS from a 2D digital facial photograph. **B)** To measure the palpebral fissure length (PFL) the User clicks the mouse on the endocanthion and exocanthion landmarks of the eye. The Software computes the PFL in mm and reports how many standard deviations above or below the mean it is by looking it up on PFL normal growth chart.

The Software was specifically designed to overcome the error often observed when PFLs were measured with a handheld ruler.[8,9] The Software was programmed to measure a PFL with the accuracy of a sliding digital caliper (the gold standard). When used in accordance with the *Software's Manual of Instructions*, the Software generates accurate measures. The Software is programmed to generate accurate measures of the PFL, innercanthal distance, and lip circularity from a 2D image of a 3D object when the digital images meet the specifications (resolution, alignment, facial expression, etc) specified in the Instruction Manual. Throughout this publication, all reference to the "Software" refers to Version 1.0[6] or Version 2.0[7], as both use the same methods for measuring the FAS facial features. The upgrade in Version 2.0 simply provided Users with access to additional PFL normal growth charts.

There has been some confusion lately in the published literature as to the Software's ability to accurately measure a PFL from a 2D photograph. Two studies have reported on the discordance of ruler, caliper, and Software measures of the PFL. One study concluded that their Software measures were often smaller than their ruler measures.[10-11] The other study concluded

their Software measures were comparable to their ruler measures, but shorter than their caliper measures.[12] Since neither study included a gold-standard measurement of the PFL, neither study could comment on the accuracy of any of the three methods of measurement. If the Software measures tended to be smaller than the ruler and caliper measures, were the Software measures correct and the ruler and caliper measures overestimated the true PFL? Or were the Software measures incorrect and the Software underestimated the true PFL? The purpose of this study was to answer these questions.

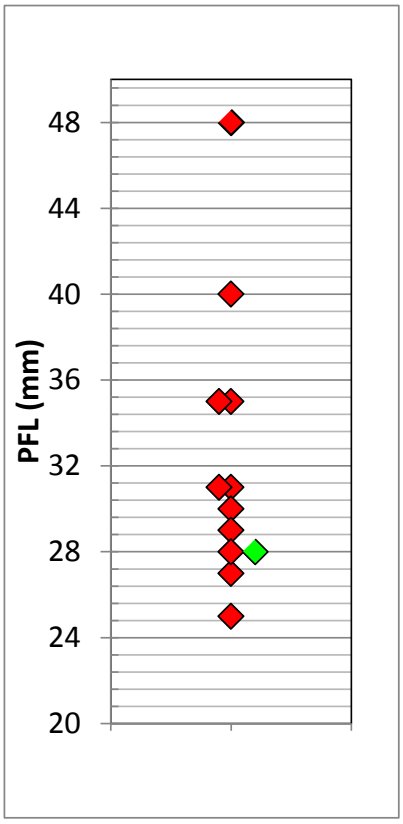
OBJECTIVES

The objectives of this study were:

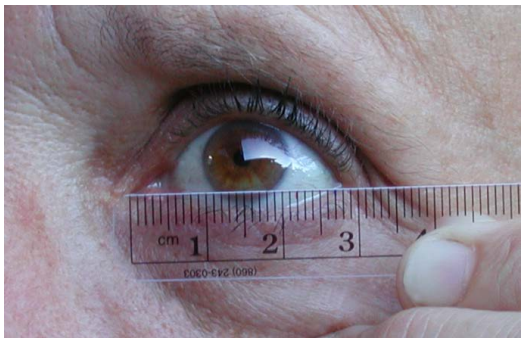
1. To demonstrate the ability of the FAS Facial Photographic Analysis Software's to accurately measure a PFL from a 2-dimensional digital facial photograph. The PFL is the distance between the endocanthion and exocanthion landmarks (Fig 2).
2. To demonstrate the frequency and magnitude of error when PFLs are measured directly by clinicians using a ruler.

It is important to clarify that this study is not assessing the accuracy of the Software for the first time, but rather demonstrating the accuracy of the Software. The accuracy of the Software was assessed and confirmed prior to its release in 2003. The Software was developed to overcome the high frequency of error known to occur when the PFL is measured directly using a ruler (Fig. 4).

Although a demonstration of the Software's PFL measurement accuracy is posted on the FAS DPN website and the website cautions clinicians about the risk of error associated with ruler measurement of the PFL[1], neither of these topics have been comprehensively addressed by the FAS DPN in the published literature. With recent inquiry into which method of PFL measurement is most accurate (ruler, caliper, or Software)[10,11] a clear demonstration of the Software's accuracy and the ruler's inaccuracy is warranted to help guide clinicians in their choice of method.



A.



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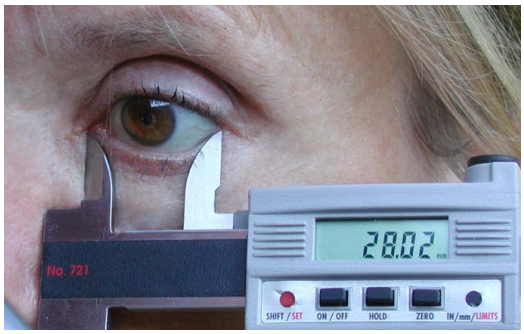
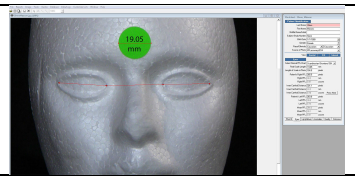
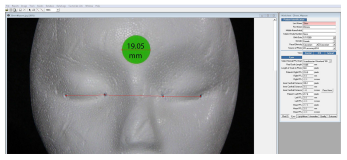
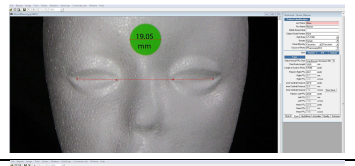
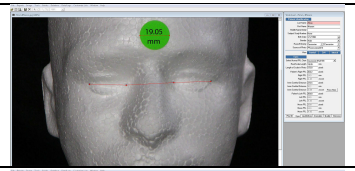
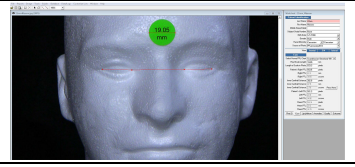
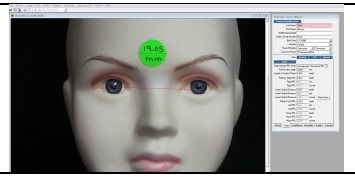
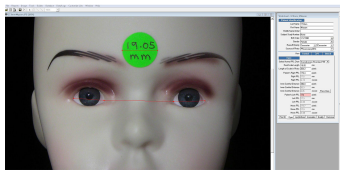
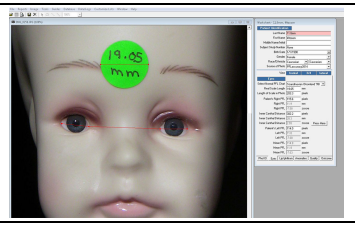
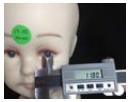
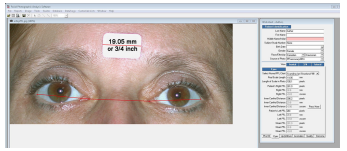


C

FIG. 4 **A**. The inherent inaccuracy of measuring a PFL with a ruler was demonstrated in an exercise in which the author's left PFL was measured by 11 clinicians using a ruler. Although measurement of a PFL with a ruler may seem straightforward (**B**), the clinicians' measures ranged from 25 mm to 48 mm (red diamonds). **C**. The true PFL was 28.02 mm (green diamond) as demonstrated with a sliding digital caliper placed directly on the endocanthion and exocanthion landmarks. USE OF A CALIPER IN THIS WAY IS VERY DANGEROUS AND SHOULD NEVER BE DONE WITH A PATIENT.

TABLE 1 Software and caliper measures of the palpebral fissure lengths (PFL) from eight mannequins and one human subject.

Mannequin	OFC (cm)	Assigned Age (yrs)	Left PFL (mm)			Right PFL (mm)			Mean PFL (mm)		Facial Image	Software PFL	Caliper PFL
			Caliper	Software	Caliper – Software	Caliper	Software	Caliper – Software	Soft ware	Caliper - Software			
Adult female	51.5	20	30	30	0	30	30.2	-0.2	30.1	-0.1			
Adolescent female 2	53	14	28	28	0	28	28	0	28	0			
Adolescent female	51.5	15	26	26.3	-0.3	26	26.1	-0.1	26.2	-0.2			
Adolescent male	51.5	15	25	24.9	0.1	25	24.9	0.1	24.9	+0.1			
Adolescent male	54.5	15	22	22.0	0	22	22.3	-0.3	22.2	-0.2			

Child female	53.5	8	19	19.3	-0.3	19.0	19.1	-0.1	19.2	-0.2			
Toddler female	47.5	2	17.8	17.9	-0.1	17.8	17.8	0	17.9	-0.1			
Infant female	39.0	0.16	11.8	11.8	0	11.8	11.9	-0.1	11.9	-0.1			
Author	54.8		28.02	28	+0.02								

OFC: occipital frontal circumference. mm: millimeters

METHODS

Objective 1: Software Accuracy

***Mannequin Heads*:** Eight life-size mannequin heads representing males and females across the lifespan (infant, child, adult) were used (Table 1). The head circumferences of the mannequins ranged from 39 to 54.5 mm, reflective of normal head circumferences for individuals infant through adult. Three mannequin heads were made from plastic and had eyes clearly painted on the face. Their PFLs were measured with calipers to be 11.8 mm, 17.8 mm, and 19.0 mm. Five mannequins were made from white Styrofoam and had facial features formed into the Styrofoam, but did not have eyes painted on the face. To accommodate this, a black, fine-tip felt marker was used to place small dots on each of the five mannequins to represent the endocanthion and exocanthion landmarks for the right and left palpebral fissure lengths. The five Styrofoam mannequins came with a variety of eye sizes ranging from 22 to 30 mm, thus the landmarks were placed to create PFLs of exactly 22, 25, 26, 28 and 30 mm, purposely spanning a range of PFL that would be observed in infants, children and adults.[5]

Caliper Measures of PFLs: The right and left PFLs were measured with a sliding digital caliper (Fig 4, Table 1). The prongs of the caliper were placed directly on the endocanthion and exocanthion landmarks of the palpebral fissure to obtain an exact (gold standard) measure of the PFL. A caliper can only serve as a gold standard of accurate measurement if the prongs of the caliper can be placed directly in contact with the 2 points in space being measured. A photograph was taken of each caliper measure to document the reading on the caliper. Human subjects were not used in this study because the gold standard measure of the PFL requires placing the prongs of the caliper directly on the endocanthion and exocanthion landmarks; a procedure that cannot be safely conducted with a human.

Facial Photograph: A frontal facial photograph of each mannequin head was obtained in accordance with the FAS Facial Photographic Analysis Software Version 2.0 Instruction Manual.[7] Briefly, a ¾ inch (19.05 mm) round paper sticker was placed between the eyebrows to serve an internal unit of measure in the digital image (Fig. 5, Table 1). A 5-megapixel digital camera was held 4 feet from the mannequin. The zoom feature was used to zoom in on the face until the head filled the camera frame (Table 1). Care was taken to obtain a frontal photograph with no vertical (tipped up or down) or horizontal (turned right or left) rotation.

To achieve this, the camera was held in the mannequin's Frankfort horizontal plane (the plane that runs through the external ear canals and the lower borders of the bony orbital rims) (Fig. 5). The camera was also aligned such that the right and left ears were equally visible. This camera alignment procedure is demonstrated in an animation posted on the FASDPN website.

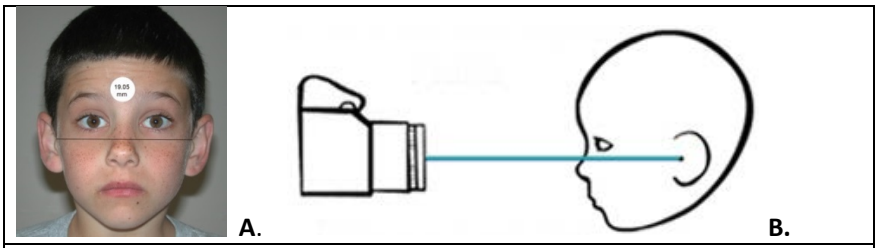


FIG. 5 A) Example of a properly aligned facial photograph. The camera is aligned in the subject's Frankfort horizontal plane (**B**. the plane (blue line) that runs through the external auditory canals and the lower borders of the bony orbital rims). When the camera is held in the subject's Frankfort horizontal plane, a line drawn between the right and left auditory canals on the facial photograph would fall along the lower boney orbital rims.

Software Measures of PFLs: Each facial image was imported into the Software for analysis. All analyses were conducted by the author. In accordance with the Software Instruction Manual, the Software's zoom feature was used to enlarge the image so the eyes and sticker covered the full width of the computer monitor (Table 1). This affords more accurate measures. To establish the measurement scale in the photo, the diameter of the paper sticker was measured. Distance in a digital image is measured in units called pixels. Pixels are the little dots of light that make up the image displayed on a computer screen. The diameter of the sticker in pixels was measured using the "single distance" tool. With the mouse the User selects the tool and clicks on the right edge of the sticker and then the left edge, bisecting the circle. This procedure establishes how many pixels is equivalent to 19.05 mm in the digital image. Next, the 3-distance tool was used to measure the right PFL, inner canthal distance (the distance between the eyes), and left PFL. With the mouse, the User selects the tool and clicks on the right exocanthion, right endocanthion, left endocanthion, and left exocanthion, in that order. In so doing, the Software records the right PFL, inner canthal distance, and left PFL in pixels. The Software then converts these three measures from pixels to mm using the pixel- to-mm conversion ratio established from measuring the diameter of the paper sticker.

***Data Analysis*:** All data was entered into SPSS[13] for analysis. The caliper measure of the PFL served as the gold standard in this study. If the Software was generating an accurate measure of the PFL, the Software measure should match the caliper measure. The Software measure of each PFL was subtracted from the caliper measure of the PFL to assess the Software's measurement accuracy. If the Software was generating an accurate measure of the PFL, the Software measure should match the caliper measure (the difference between the two measures would be zero). A negative outcome would document the Software underestimated the PFL. A positive outcome would document the Software overestimated the PFL.

Objective 2: Ruler Variability

The frequency and magnitude of error observed when clinicians use a ruler to measure the PFL was demonstrated by comparing: A) Ruler measures to caliper measures; B) Ruler measures to Software measures; and C) Ruler measures obtained by two clinicians. All data collection and analysis had Human Subjects Review Board approval.

A. *Ruler versus Caliper*

In 2000, the author invited 11 clinicians at the University of Washington to participate in an exercise in which they were asked to measure her left PFL to the best of their ability with a 15 cm plastic ruler (Fig. 4). These clinicians were selected because measuring PFLs was a routine part of their clinical practice. The only instruction they received was to view the image in Fig. 4B documenting the endocanthion and exocanthion landmarks that define the PFL. They were asked to write the PFL measure on a piece of paper and insert it into an envelope. The identity of the clinicians was not recorded. The true length of the palpebral fissure (obtained with a caliper) was shared with the clinician after they placed their measure in the envelope. They were asked not to reveal what measure they obtained, to maintain the anonymity of the exercise.

Data Analysis: The caliper measure of the author's left PFL and ruler measures obtained by 11 clinicians were plotted to illustrate inter-rater variability (Fig. 4).

B. *Ruler versus Software*

Over the past 20 years in the WA FAS DPN clinics, 1,027 patients had their PFLs measured by one of 21 different medical doctors using a 15 cm ruler. All 1,027 patients also had a digital facial photograph taken that was measured by the author using the FAS Facial Photographic Analysis Software. The 1,027 patients were 43% female and were on average 8.5 (5.5 SD) years of age. They ranged in age from 2 months to 48 years of age, with 92% under the age of 15 years.

Data Analysis: To compare the ruler versus Software measures of each patient's PFLs, the mean of the right and left PFLs derived by the Software was subtracted from the mean of the right and left PFLs obtained by the clinician using a

ruler (ruler mean PFL minus Software mean PFL). A negative difference reflected the Software measure of the mean PFL was longer than the ruler measure. A positive difference reflected the Software measure of the mean PFL was shorter than the ruler measure. Since the smallest unit of measure on the ruler is 1 mm (Fig. 2) and the smallest unit of measure using the Software is 0.1 mm, the ruler measure was considered a match to the Software measure if the ruler measure was within -0.9 to +0.9 mm of the Software measure. The outcomes were plotted by documenting what proportion of subjects had PFL measures that were < 1, 1, 2, or 3 or more mm different between the ruler and Software measures. Differences were categorized into 1 mm bins because 1 mm is the smallest unit of measurement demarcated on the ruler. An error of 1 mm is equivalent to an error of roughly three quarters of a SD on a normal growth chart for PFL.[5] A 1 mm error could result in an incorrect diagnosis under the umbrella of FASD. For example, if a 13 year old girl had a PFL that was truly 27 mm, her PFL would fall 0.6 standard deviations below the mean for a girl her age using the Stromland normal PFL growth charts[5]. The FASD 4-Digit Code would classify this PFL as being in the normal range (PFL ABC-score = A). If the clinician incorrectly measured her PFL by -1 mm, her 26 mm PFL would appear to be 1.3 SDs below the mean. The FASD 4-Digit Code would classify this PFL as being in the moderately short range (PFL ABC-score = B). If the clinician incorrectly measured her PFL by 2 mm, her 25 mm PFL would appear to be 2.0 SDs below the mean. The FASD 4-Digit Code would classify this PFL as being in the significantly short range (PFL ABC-score = C). Thus, a 1 mm error can incorrectly classify the PFL in the PFAS range and a 2mm error can incorrectly classify the PFL into the FAS range.

It is important to note that in the absence of a gold-standard measure (e.g., a caliper measure of the PFL), if a difference is observed between the ruler and Software measures, one of three conclusions can be drawn: 1) the ruler measure is incorrect; 2) the Software measure is incorrect; or 3) both measures are incorrect. The outcome of Objective 1 will help determine which of these three outcomes is supported.

C. *Ruler versus Ruler*

241 patients that had their PFLs measured with a ruler by both the medical doctor and the author. The 241 patients were 44% female and were on average 8.9 (5.1 SD) years of age. They ranged in age from 1.3 to 40 years of age, with 93% under the age of 15 years.

Data Analysis: To compare the two ruler measures of a patient's PFLs, the medical doctor's measure of the patient's left PFL was subtracted from the author's measure of the patient's left PFL (author's measure of PFL minus doctor's measure of PFL). A negative difference reflected the doctor's measure of the left PFL was longer than the author's measure. A positive difference reflected the doctor's measure of the left PFL was shorter than the author's measure. Since the smallest unit of measure on the ruler was 1 mm, the two clinicians' measures of the PFL were considered a match if they were within plus or minus 0.9 mm of one another. The outcomes were plotted by documenting what proportion of subjects had PFL measures that were < 1, 1, 2, or 3 or more mm different between the two ruler measures.

RESULTS

Objective 1. Software Accuracy:

The Software produced right and left PFL's that either matched or were no more than 0.2 mm different from the right and left PFLs measured with the calipers. These outcomes did not vary by gender, age (infant, child, adult), OFC (39-54.5 cm), or PFL (11.8 -30.0 mm) (Table 1).

Objective 2A. Ruler Variability:

Ruler versus Caliper

The PFL measures recorded by the 11 clinicians ranged from 25 mm to 48 mm (Fig. 4). The true PFL measured with a caliper was 28.02 mm. Eight of the 11 physician measures were incorrect by 2 to 16 mm. .

Objective 2B. Ruler Variability:

Ruler versus Software

One thousand twenty-seven patients across the full age span (infant to adult) had their PFLs measured by both the medical doctor using a ruler and from a photograph using the Software (Fig.

6). These measures involved 21 different doctors over 21 years. The doctor's measure with the ruler was within 1 mm of the Software measure 44.7% of the time. The two measures differed by 2 or more mm 21.1% of the time. When the ruler and Software PFL measures were compared among the subset of 166 patients that were under the age of 4 years, the distribution of error was near identical to that of the entire age spectrum. Since Objective 1 demonstrated the Software accurately derives a PFL from a 2D facial photo when the Software is used properly (high quality photos with proper alignment) and Objective 2A demonstrated high variability in ruler measures, the discordance between the ruler and Software measures presented here were most likely the result of incorrect ruler measures.

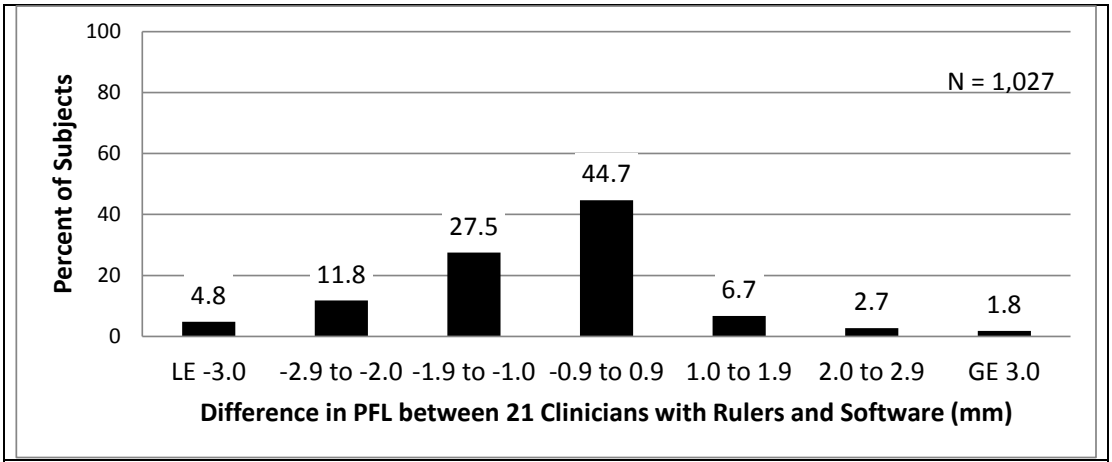


FIG. 6 ***Objective 2B*** The prevalence and magnitude of discordance is illustrated when the PFLs of 1,027 patients were measured from 2D facial photos using the FAS Facial Photographic Analysis Softare and measured by one of 21 medical doctors using a 15 cm ruler. The columns represent how often the ruler measure minus the Software measure was 1 or more mm diffferent. A negative difference reflects the ruler measure of the PFL was smaller than the Software measure of the PFL. A positive difference reflects the ruler measure was larger than the Software measure. Differences less than 1 mm were considered a match since 1 mm was the finest level of measurement marked on the ruler.

Of the 1,027 patients who had their PFL measured by a clinician using a ruler, 297 also had their PFL measured by the author. The 297 patients were 42% female and were on average 8.9 (5.0 SD) years of age. They ranged in age from 8 months to 40 years of age, with 94% under the age of 15 years. When the author's ruler measures were compared to the Software measures, 84.9 % of the ruler measures were less than 1 mm different from the Software measures (Fig. 7). Less than 2% were 2 or more mm different from the Software.

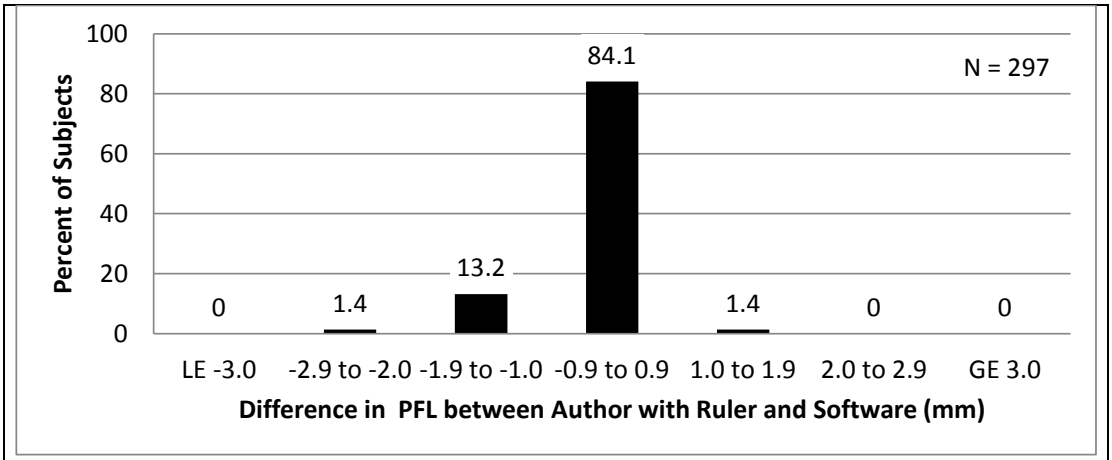


FIG. 7. ***Objective 2B:*** The prevalence and magnitude of discordance is illustrated when the PFLs of 297 patients were measured from 2D facial photos using the FAS Facial Photographic Analysis Softare and measured by the author using a 15 cm ruler. The columns represent how often the ruler measure minus the Software measure was 1 or more mm diffferent. A negative difference reflects the ruler measure of the PFL was smaller than the Software measure of the PFL. A positive difference reflects the ruler measure was larger than the Software measure. Differences less than 1 mm were considered a match since 1 mm was the finest level of measurement marked on the ruler.

As documented above, it is standard procedure in the University of Washington FAS DPN clinic to measure a patient's PFL directly with a ruler and from a photo using the Software. Due to the confirmed accuracy of the Software, we use the Software measure for the diagnosis. The ruler measure simply serves as an opportunity for the clinician to hone their skills with a ruler in the event they have to measure a patient without access to the Software. To demonstrate the value of this training, Fig. 8 documents the improvement in skill across three clinicians. The mean difference between the ruler and Software measures across all patients measured each year are presented from 2004 through 2011. These 320 patients were 42% female and were on average 8.1 (5.1 SD) years of age. They ranged in age from 2 months to 40 years of age, with 93% under the age of 15 years. When the Software was first introduced in the clinic in 2003, PFLs measured with a ruler were on average 2 mm discordant from the Software measures. Over time, the ruler measures moved into the green zone, documenting the ruler measures on average were more concordant (within 1 mm) of the Software measures. But it is important to point out that the 1 SD error bars (Fig. 8A) and the plot of individual patient measures (Fig. 8B) document the clinicians' individual measures still had an unacceptable level of variation from the Software measures, even if on average their measures were improving over time. Over half of the individual measures fell outside the green lines (were more than 1 mm discordant from the Software measure).

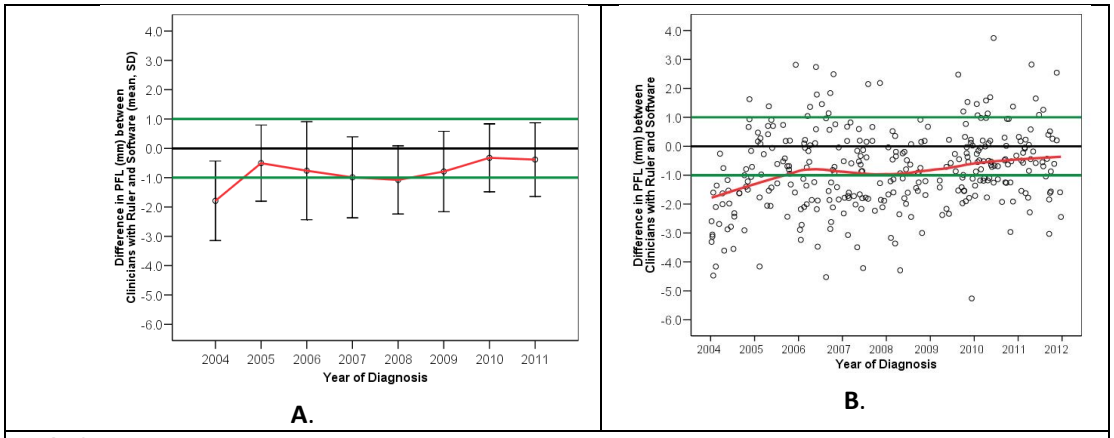


FIG. 8 ***Objective 2B:*** The difference in the ruler minus Software measure of the PFL is plotted annually across three clinicians and 320 patients. Ruler measures were collected at the beginning of the FASD diagnostic evaluation. Software measures were not available to compare to until the end of the evaluation. A. On average, the accuracy of PFL measures obtained with a ruler improved over time when the three clinicians had Software measures to compare to their ruler measures. The mean difference in the ruler minus Software measure of all PFLs collected each year are plotted with 1 SD error bars. The zone between the green lines reflects the perferred level of accuracy (less than 1 mm difference between the ruler and Software measures). The Software was introduced into the Clinic in 2003. Even though the mean difference tends to fall between the green lines (Fig. 8A), the magnitude of difference between the ruler and Software measures for each indivdiual patient (Fig 8B) continued to show far too much variability with over half the indivdual measures falling outside the green zone.

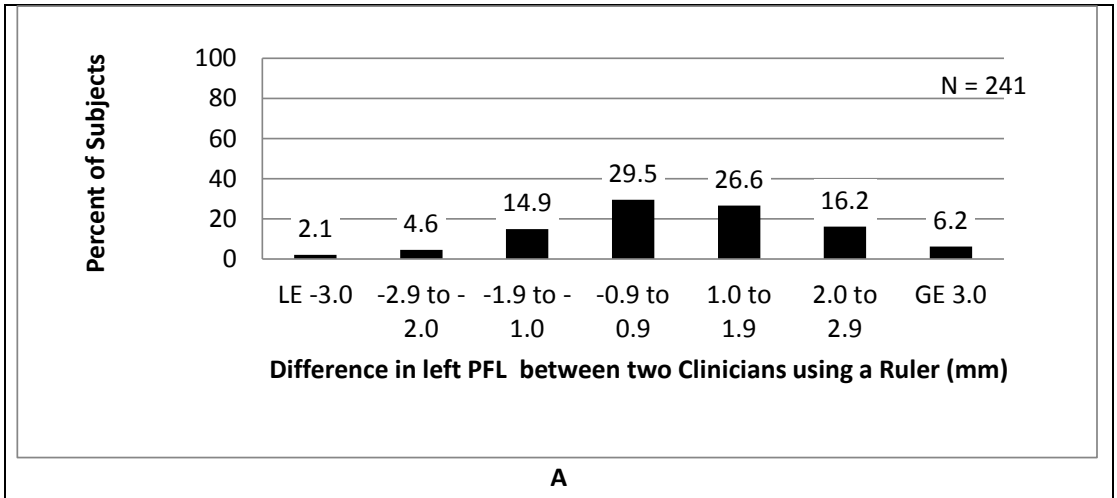


FIG. 9 ***Objective 2C:*** Ruler vs Ruler Measure. The prevalence and magnitude of discordance is illustrated when the left PFLs of 241 patients were measured by both the author and the medical doctor using a 15 cm ruler. The columns represent how often the two measures were 1 or more mm diffferent. A negative difference reflected the doctor's measure of the left PFL was longer than the author's measure. A positive difference reflected the doctor's measure of the left PFL was shorter than the author's measure. Since the smallest unit of measure on the ruler was 1 mm, the two clinicians' measures of the PFL were considered a match if they were within plus or minus 0.9 mm of one another.

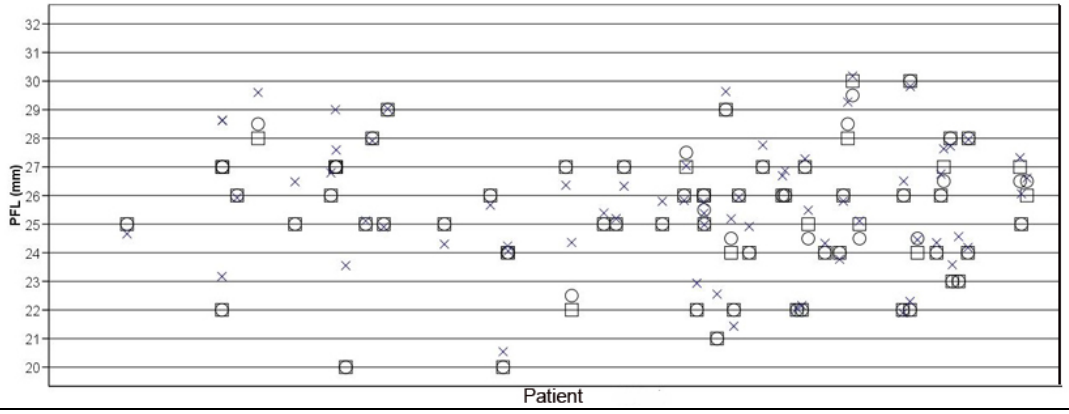


FIG. 10 ***Objective 2C***: Ruler vs Ruler vs Software Measures of the 71 (29.5%) patients in Fig. 9 with concordant ruler measures (measures within 0.9 mm of one another). It is important to note that when the two PFL measures obtained with a ruler were concordant (within 1 mm of one another), this does not confirm the PFL measures were correct. The two measures could be concordant and both incorrect. This figure documents that15 of the 71 patients with concordant PFL ruler measures have one or more ruler measures that are discordant (greater than 1 mm different) from the Software measure Key: Circle = Clinician 1. Square = Clinician 2. X = Software measure.

Objective 2C. Ruler Variability:

Ruler versus Ruler

When patients (n = 241) had their PFLs measured by two different individuals (the medical doctor and the author), the PFL measures were within 1 mm of one another 29.5% of the time (Fig. 9). One mm is the smallest unit of measure marked on the ruler. The PFL measures were 2 or more mm different 29.1 % of the time. Most importantly, the measures were discordant (1 or more mm different) 70.5% of the time. Despite the absence of a gold standard (caliper) measure of the patients' PFLs, one can still conclude that at least 70.5% of the patients had their PFL measured incorrectly by at least one of the two clinicians. It is also important to note that when the two PFL measures obtained with a ruler were concordant (within 1 mm of one another), this does not confirm the PFL measures were correct. The two measures could be concordant and both incorrect. The majority of these 241 patients also had their PFLs measured from a photo using the Software. Figure 10 documents how often the two ruler measurements matched the Software measurement among the 71 (29.5%) patients with concordant ruler measurements. If the Software measures are assumed accurate (as demonstrated in Objective 1), then 15 of the 71 patients with concordant PFL ruler measures have one or more ruler measures that are discordant (greater than 1 mm different) from the Software measure. This would suggest that 77% of the patients had their PFLs measured incorrectly (greater than 1 mm error) with a ruler by at least one of the two clinicians.

DISCUSSION

The data presented in this report confirm that the FAS Facial Photographic Analysis Software generates accurate measures of the PFL from a 2D digital facial photograph when compared to the gold standard. The gold standard was a sliding digital caliper with the caliper prongs placed directly in contact with the endocanthion and exocanthion landmarks that define the PFL. This measurement accuracy was confirmed prior to the

release of the Software. The release of the Software was contingent on its ability to generate accurate measures of the FAS facial features.

The data presented in this report also demonstrate the prevalence and magnitude of error when a patient's PFL is measured directly with a ruler. The prevalence and magnitude of this error was well known prior to the release of the Software.[4,8,9] One of the primary reasons the Software was developed was to overcome this error.

In 2004, a document was posted on the FAS DPN website demonstrating the Software's ability to accurately measure a PFL. The author's PFLs were measured with a ruler, with a caliper, and with the Software (Table 1). Photos of each measure were taken to document the outcomes. These data are included in this report (Fig. 4) to demonstrate the PFL is measured accurately whether obtained from a mannequin or human.

Two other investigative teams[10-12] have reported on the discordance of ruler, caliper, and Software measures of the PFL. Since neither study included a gold-standard measurement of the PFL, neither study could comment on the accuracy of any of the three methods of measurement. Inclusion of a gold standard of measurement in our study allowed us to confirm the technical accuracy of the FAS Facial Photographic Analysis Software. This confirmation provides some helpful context for comparing our outcomes to those reported in these two previous studies.

In the first study, the PFLs of 40 children (2 months to 15 years old) referred for a FASD evaluation were measured using both a ruler and the Software.[10,11] The number of clinicians involved was not reported. Avner et al[10,11] reported their Software measures of the PFLs were on average 2 mm shorter than their ruler measures across all 40 children; and 3 mm shorter among the subset of 21 children under 4 years of age. These contrasts are 3 to 4-fold greater than observed in our study. Our Software measures were on average 0.7 mm longer (not shorter) than the ruler measures across 1,027 patients measured by one of 21 clinicians, and 0.9 mm longer among the subset of 166 patients under 4 years of age. Since our study demonstrated the Software measures a PFL within 0.2 mm of a gold standard caliper measure in a properly standardized photograph, the 2.0 mm to 3.0 mm contrast between their ruler and Software measures cannot be explained by Software error. Contrasts that are 2.0 mm to 3.0 mm in magnitude are the result of User error. The investigators discuss the types of User error that may occur when measuring a PFL with a ruler (e.g., patient cooperation, examiner's skill), but there are also opportunities for User error when measuring a PFL with the Software (e.g. poor photo quality, eyes not fully open, inaccurate identification of landmarks by User, etc). These sources of error are discussed more fully below. The investigators went on to compare the number of children identified with PFLs 2 or more SDs below the mean using the ruler and Software methods of measurement. The ruler method identified 9 children; the Software method identified 14 children.

The investigators concluded "*The method of computer-assisted measurement tends to underestimate the true length and, hence, over diagnose short palpebral fissure, especially in children under four years old "*. The study methodology does not support this conclusion because the study did not have a measure of the "true" length of the palpebral fissure. The 'true' length of the palpebral fissure would require use of a gold standard method of measurement. The study did not incorporate a gold standard measure of the PFL. The investigators also computed sensitivity and specificity and reported "*Since the photographic method tends to overestimate the number of short PFLs (sensitivity=100%, specificity=64%), it is likely to over-diagnosis FAS. Therefore, telediagnosis would be most useful if it were followed by direct measurement, (since the photographic method alone produced false positives, but no false negatives*)." Once again the study methodology does not support this conclusion. Sensitivity and specificity require a gold standard measure of the PFL to represent the "true positive". The study had no gold standard measure of the PFL. Thus the study cannot compute the sensitivity or specificity for the ruler or the Software. Our current study demonstrates that it is highly unlikely that direct measurement of the PFL with a ruler would provide a more

accurate measure than the Software when the software is used properly.

In the second study a single clinician measured the PFLs of 50 children and 50 adults using all three tools (Software, ruler, and caliper).[12] Cranston et al[12] reported their Software measures were concordant with their ruler measures 42% of the time. This is consistent with our findings. We observed concordance between our Software measures and ruler measures 44.7% of the time across 1,027 patients measured by one of 21 clinicians. Cranston et al[12] also reported their Software measures were concordant with their caliper measures only 18% of the time. This is in stark contrast with our results. We observed 100% concordance between our Software and caliper measures of the PFL. The most likely reason their Software and caliper measures were discordant was because the Software was measuring the actual PFL and the caliper was measuring an approximation of the PFL. This is illustrated in their Figures 2 and 1B, respectively. Since their subjects were human, they could not obtain an accurate PFL with a caliper because it was too dangerous to place the prongs of the caliper directly on the individual's endocanthion and exocanthion landmarks that define the PFL. We used mannequins in our study to overcome this limitation.

Although the present study has demonstrated that the FAS Facial Photographic Analysis Software is programmed to accurately measure a PFL from a properly standardized 2D digital facial photograph, this does not mean that every measure of a PFL using the Software is accurate. The PFL measures obtained using the Software are only as accurate as the quality of the photo and the skills of the Software User. To minimize User error, the Software comes with detailed instructions and a practice case "John Doe" (Fig. 5A). The practice case serves two purposes. 1) It provides the User with an example of what a perfect set of standardized digital photographs (frontal, ¾, and lateral views) looks like. John Doe's photos display the following qualities: They are focused, well lit, high resolution, and properly aligned. John has no smile, his lips are gently closed, and his eyes are fully open. These qualities are not only important for accurate photo analysis of FAS facial features, they are also important when the facial features are being measured directly with a ruler and Lip-Philtrum Guide. 2) The Software also provides the User with an opportunity to practice measuring John Doe's photos to confirm they have the necessary skills to derive accurate measures. The Software comes with John Doe's photo set fully and accurately measured and permanently stored in the Software. When measuring facial features with the Software, whether for clinical or research purposes, it is imperative the User ensure and report the quality of the photos measured. It is also important they confirm they can measure John Doe's' photoset with high inter-rater reliability (i.e., their measures of John Doe's facial features match the gold-standard measures recorded in the Software). They should also confirm they have high test-retest reliability (i.e., they obtain the same PFL and lip circularity measures across multiple photos they have taken of a single individual).

The Software is particularly helpful in obtaining accurate facial measures from small moving targets like toddlers. The photo not only renders the moving target motionless, but a toddler is far more likely to let you approach them with a camera than a PFL ruler. While it may prove challenging at times to take a properly aligned photo of a toddler on the move, there are a number of tricks that will help you achieve this. Conduct the photo session in a small quiet room. Take multiple photos to ensure capture of the eyes and lips in proper repose. Keep in mind the eyes can be measured from one photo and the lips from another photo, if both could not be captured properly in a single photo. And if all else fails, simply set your camera to video mode, record 15-20 seconds of video, and capture the single frame or two where the facial features are in proper repose. Perhaps the greatest advantage of the photo over direct measure is the photo provides a permanent record which will prove invaluable for medical and research purposes.

CONCLUSIONS

In summary, the FAS Facial Photographic Analysis Software measures the PFL with the same accuracy as a sliding digital caliper, as it was programmed to do. Direct measurement of the PFL with a ruler is highly prone to error, even among clinicians who have measured hundreds of PFLs. Direct measurement of the PFL with a caliper is far too dangerous at any age, and should not be used.

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The essential role of growth deficiency in the diagnosis of fetal alcohol spectrum disorder

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Abstract

Background: Laboratory studies confirm prenatal alcohol exposure (PAE) causes growth deficiency (GD). GD has traditionally been a core diagnostic feature of fetal alcohol spectrum disorders (FASD), but was removed from the Canadian and Australian FASD diagnostic guidelines in 2016. This study aimed to empirically assess the clinical role and value of GD in FASD diagnosis.

Methods: Data from 1814 patients with FASD from the University of Washington Fetal Alcohol Syndrome Diagnostic & Prevention dataset were analyzed to answer the following questions: 1) Is there evidence of a causal association between PAE and GD in our clinical population? 2) Is GD sufficiently prevalent among individuals with PAE to warrant its inclusion as a diagnostic criterion? 3) Does GD aid the diagnostic team in identifying and/or predicting which individuals will be most impaired by their PAE?

Results: GD significantly correlated with PAE. GD was as prevalent as the other core diagnostic features (facial and CNS abnormalities). GD occurred in all FASD diagnoses and increased in prevalence with increasing severity of diagnosis. The most prevalent form of GD was postnatal short stature. GD was as highly correlated with, and predictive of, severe brain dysfunction as the FAS facial phenotype. Individuals with GD had a two to three-fold increased risk for severe brain dysfunction. Sixty percent of patients with severe GD had severe brain dysfunction. GD accurately predicted which infants presented with severe brain dysfunction later in childhood

Conclusions: GD is an essential diagnostic criterion for FASD and will remain in the FASD 4-Digit Code.

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Introduction

Fetal alcohol syndrome (FAS) is a birth defect syndrome caused by maternal consumption of alcohol during pregnancy. The term FAS was first coined in 1973 [1,2], and is characterized by growth deficiency (GD), a specific cluster of minor facial anomalies, and central nervous system (CNS) structural and/or functional abnormalities. Not all individuals exposed to and damaged by prenatal alcohol exposure (PAE) have FAS. Rather, PAE causes growth, facial, and CNS abnormalities that each present along a continuum of abnormality from mild, moderate, to severe [3,4]. Taken together, these outcomes present along a continuum of diagnoses under the umbrella of fetal alcohol spectrum disorder (FASD): FAS, partial FAS (PFAS), static encephalopathy/alcohol-exposed

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(SE/AE), and neurobehavioral disorder/alcohol-exposed (ND/AE).

GD has traditionally been a core diagnostic feature of FAS [5]. The original small group of patients from which the term was first derived was identified, in large part, because of their GD [6,7]. It is common for a new condition/syndrome to be recognized among the most severe cases. Thus, over time, it became clear that FAS was reflective of the most severe end of the fetal alcohol spectrum. Decades of laboratory and clinical-based studies unequivocally confirmed that PAE causes GD [8–12]. Nevertheless, not all individuals with PAE present with GD, and not all individuals with GD have PAE, so the question was raised as to whether GD should have been included as a core diagnostic feature of FAS.

In the 2016 revisions of the Canadian [13] and Australian [14] FASD diagnostic guidelines, GD was removed as a diagnostic criterion for FASD. The Canadian guidelines present the following justifications for removing GD:

1. Growth deficiency is neither sensitive nor sufficiently specific to indicate a diagnosis of FASD.
2. The predictive value of growth deficiency has been questioned.
3. FAS was 'discovered' in 1973 because a group of children referred to a clinic for growth deficiency were later found to have other features of what is now known as FAS.

The purpose of this study was to empirically assess the role and value of GD in FASD diagnosis. Laboratory studies confirm PAE causes GD. Is there evidence of a causal association between PAE and GD in our clinical population? Is GD sufficiently prevalent among individuals with PAE to warrant inclusion as a diagnostic criterion? The most debilitating aspect of FASD is CNS dysfunction. Does the presence of GD aid the clinical team in identifying and predicting which individuals will be most impaired by their PAE? The results of this study will be used to determine whether the FASD 4-Digit Diagnostic Code [3,4] described below maintains or removes GD as a core FASD diagnostic feature.

Methods

Data from 1814 patients evaluated consecutively from January 1993 through December 2012 at one of the University of Washington Fetal Alcohol Syndrome Diagnostic and Prevention (WA FASDPN) clinics were used in this study. The data source was the WA FASDPN research database. All patients evaluated at the WA FASDPN clinics are invited to have their FASD clinical data entered into the WA FASDPN research database, at the time of their diagnostic evaluation, for use in future research studies. Patient/caregiver consent is obtained in accordance with University of Washington Human Subjects Division oversight and approval. All patients were diagnosed in accordance with (or upgraded to) the 2004 FASD 4-Digit Diagnostic Code [3,4].

The FASD 4-Digit Code is described in full by Astley [3,4]. Briefly, the four digits reflect the magnitude of expression of the four key diagnostic features of FASD, in the following order: 1) growth deficiency, 2) FAS facial phenotype, 3) CNS structural/functional abnormalities, and 4) prenatal alcohol exposure (Figure 2A). The magnitude of expression of each feature is ranked independently on a four-point Likert scale, with 1 reflecting complete absence of the FASD feature, and 4 reflecting a strong 'classic' presence of the FASD feature. Each Likert rank is specifically case-defined. A total of 102 4-Digit Codes fall broadly under the umbrella of FASD. These codes cluster under four clinically meaningful FASD diagnostic subcategories: fetal alcohol syndrome (FAS), diagnostic categories A and B; partial FAS (PFAS): diagnostic category C; static encephalopathy/alcohol-exposed (SE/AE), diagnostic categories E and F; and neurobehavioral disorder/alcohol-exposed (ND/AE), diagnostic categories G and H. Each diagnosis has a version with and without GD (Table 1).

The 4-Digit Code takes a unique approach to ranking GD, placing emphasis on height deficiency over weight deficiency. Below are the instructions provided to clinicians for how to document growth deficiency using the FASD 4-Digit Code [3].

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Table 1. FASD 4-Digit Code diagnoses with and without growth deficiency

With growth deficiency	Without growth deficiency
fetal alcohol syndrome (Categories A, B)	partial fetal alcohol syndrome (Category C)
static encephalopathy / alcohol-exposed (Category E)	static encephalopathy / alcohol-exposed (Category F)
neurobehavioral disorder / alcohol-exposed (Category G)	neurobehavioral disorder / alcohol-exposed (Category H)

What type of GD are we looking for?

We are looking for GD characteristic of a teratogenic insult, not of postnatal environmental factors such as nutritional deprivation or chronic or acute illness. We want to answer the question *'What is the patient's growth potential after controlling for parental height and postnatal environmental influences?'* GD of teratogenic origin is likely to present as a relatively consistent impairment over a period of time (i.e., the patient's growth follows the normal curve, but is below genetic expectation for family background). In contrast, GD caused by postnatal environmental influences is likely to present as periodic fluctuations in the curve. Separating the two growth patterns requires astute clinical judgment.

The method described below allows one to rank a patient's overall growth pattern on a single four-point Likert scale with 1 equal to 'normal' and 4 equal to 'significantly deficient'. Not all patients will have complete growth curves available; therefore, a guide is provided below to prioritize the ranking of the patient's growth over a lifetime.

How to measure and rank growth

A. The height percentile should be age-adjusted and gender-adjusted. Because there is a significant genetic component in attained stature, adjustment for mid-parent stature is also recommended when both parents' heights are known.

B. The weight percentile should be age-adjusted and gender-adjusted. Weight is not adjusted for height. Valid growth charts should be used. We recommend electronic computation of percentiles for increased accuracy. The FASDPN clinic uses the Hall [15] birth weight and length growth charts for gestational age; World Health Organization (WHO) [16] height and weight growth charts for children 0–2 years of age; the WHO [16] occipital–frontal circumference (OFC) charts for children 0–5 years of age; the Centers for Disease Control (CDC) 2000 [17] height and weight growth charts for patients 2 years of age and older, and the Nellhaus [18] head circumference growth charts for children 5–18 years of age.

C. For ranking purposes, the growth record is separated into two parts:

1. Prenatal growth (birth measures)

2. Postnatal growth (all measures collected after birth, i.e. infancy through adulthood)

Select the part of the growth record with the greatest deficiency in the height percentile.

If the prenatal height percentile is lower than all postnatal height percentiles, proceed to section D for instructions on how to rank prenatal growth.

If any of the postnatal height percentiles are lower than the prenatal height percentile, select the point or consecutive points in the growth record that reflect the lowest height percentiles that cannot be attributed to postnatal environmental influences such as nutritional deprivation or chronic illness. If the height deficiency is reflected in a series of points in the growth record, as opposed to a single point, rank the level of deficiency based on the percentile range where the majority of the points fall. Proceed to section D for instructions.

Table 2. Deriving the ABC-Score for growth

	Circle the ABC-Scores for:	
Percentile range	Height	Weight
≤ third	C	C
>third and ≤ 10th	B	B
>10th	A	A

D. Rank the level of deficiency of the height and weight percentiles, for the part of the growth record with greatest deficiency in the height percentile by

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circling A, B, or C in the ABC-Score table at the bottom of page 1 of the FASD Diagnostic Form (Table 2).

The height and weight percentiles selected for ranking should be matched sets. For example, if the height at 10 years of age is selected for ranking, the corresponding weight percentile at 10 years of age should also be selected for ranking.

E. Next, refer to Table 3 to determine the 4-Digit Diagnostic rank of the Height–Weight ABC-Score recorded in Table 2. Transfer the resulting 4-Digit Diagnostic rank for growth to the 4-Digit Diagnostic Code Grid at the top of page 1 of the FASD Diagnostic Form.

Table 3. Converting the Growth ABC-Score to a 4-Digit Diagnostic Rank for growth

4-Digit diagnostic Rank	Growth deficiency Category	Height–weight ABC-Score combinations*	Percentile translation
4	Severe	CC	Height and weight ≤ third
3	Moderate	CB, BC, CA, AC	Height or weight ≤ third
2	Mild	BA, BB, AB	Neither height nor weight < third and both not > 10^{th}
1	None	AA	Height and weight > 10^{th}

*The ABC-Scores outlined in dark borders are defined by the information provided in the surrounding cells

Statistical analyses

Descriptive statistics (means, standard deviations (SD), valid percentages) were used to profile the study population. Chi-squared and Fisher Exact tests were used to compare groups and linear trends across groups for outcomes measured on nominal or ordinal scales. One-way analysis of variance (ANOVA) with Student–Newman–Keuls (SNK) multiple comparison posthoc tests were used to compare means and detect linear trends across three or more groups when outcomes were measured on a continuous scale. T-tests and paired T-tests were used to compare means between two groups for independent or paired subject groups. Logistic regression (forward stepwise with *P*-value for entry = 0.05 and *P*-value for removal = 0.10) was used to determine the odds of severe CNS dysfunction (CNS Rank 3) among patients with growth deficiency, FAS facial features, and/or microcephaly. Logistic regression was also used to assess the association between PAE and prenatal and postnatal growth deficiency after adjustment for prenatal tobacco exposure. This study had 80% power at a 95% level of confidence to detect a 50% increase in the odds of a classification of CNS Rank 3 (odds ratio (OR) = 1.50) for subjects with growth deficiency or FAS facial features relative to subjects without growth deficiency or FAS facial features.

Results

Study population

The study population included 1814 individuals with PAE diagnosed across the full spectrum of FASD (Table 4, Figure 1). Ages ranged from infant to adult (0.2 to 50.9 years of age) with 60% of subjects being of school-age (6–18 years old). The population was 42% female and 48% Caucasian.

Prevalence and profile of GD

Thirty-five percent of subjects presented with height and/or weight ≤ 10^{th} percentile, with postnatal short stature the most common form of GD.

The GD criterion for FAS is commonly defined by height and/or weight ≤ 10^{th} percentile at any time across the lifespan (Astley, 2011). Four key measures documenting growth are age-adjusted and gender-adjusted percentiles for birth length, birth weight, height at diagnosis, and weight at diagnosis.

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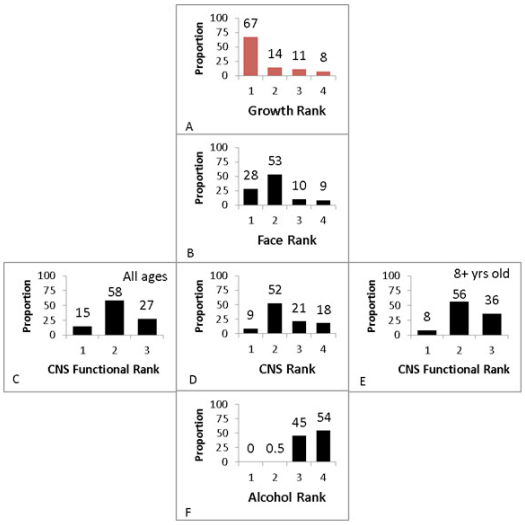

Figure 1. FASD 4-Digit Code Ranks for growth, face, central nervous system , and alcohol for 1814 subjects

Bars reflect the proportion of the population receiving Ranks 1–4 for each diagnostic feature. Face Ranks: 1 = no features; 2 = 1 or 2 features; 3 = 2.5 features; 4 = all 3 FAS facial features. Central nervous system (CNS) Ranks: 1 = normal function; 2 = moderate dysfunction; 3 = severe dysfunction; 4 = structural brain abnormalities. Alcohol Ranks: 1 = no prenatal exposure; 2 = unknown exposure; 3 = confirmed exposure to moderate levels; 4 = confirmed exposure to high levels. CNS functional Ranks: subjects with CNS Rank 4 are reclassified in accordance with their functional CNS Rank (1, 2 or 3). CNS functional Rank is presented across all ages (N = 1814). Fifty-two percent of the population was too young (< 8 years old) at the time of diagnosis to confirm or rule out CNS Rank 3 classification, thus the 27% CNS Rank 3 is an underestimate of the true prevalence of severe dysfunction. To portray a more accurate prevalence of severe CNS dysfunction (36%) observed in this alcohol-exposed population the CNS functional Ranks for the 870 subjects aged 8 years and older at the time of diagnosis is presented.

When each of these measures was assessed independently, 5.7–11.6% were ≤ third percentile, and 14.0–24.4% were ≤ 10th percentile (Table 5). GD criteria for FAS, however, require these four measures be assessed collectively (e.g., what proportion of subjects present with height and/or weight ≤ 10th percentile at any time across the lifespan?). When viewed collectively, the prevalence of GD increased.

Table 4. Study population (N = 1,814): demographic and clinical characteristics

Characteristic	N	Valid %
Gender		
Female	760	41.9
Race		
Caucasian	872	48.3
African American	139	7.7
Native American/Canadian	158	8.7
Other including mixed race	637	36.6
Unknown race	8	--
Age at diagnosis (years)		
0–2.9	226	12.5
3–5.9	420	23.2
6–7.9	297	16.4
8–12.9	508	28.0
13–18.9	281	15.4
19–51	82	4.5
Mean (SD) min–max	8.9 (6.1) 0.2–50.9	
*FASD diagnoses**		
FAS (AB)	82	4.5
PFAS (C)	123	6.8
SE/AE (EF)	504	27.8
ND/AE (GH)	943	52.0
SP/AE (I)	40	2.2
No abnormalities/AE (J)	122	6.7
Reported prenatal alcohol exposure		
First trimester only	224	15.7
First and second trimesters only	183	12.9
All three trimesters	970	68.2
Other trimester combinations	46	3.2
1–3 days per week	401	41.5
4–6 days per week	192	19.9
Daily	373	38.6

*FASD 4-Digit Code nomenclature: FAS, fetal alcohol syndrome; PFAS, partial FAS; SE/AE, static encephalopathy/alcohol-exposed; ND/AE: neurodevelopmental disorder/alcohol-exposed; SP/AE: sentinel physical findings/alcohol-exposed. Sentinel physical findings include growth deficiency and/or FAS facial features at the Rank 3 or 4 level

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Eighteen percent of patients presented with growth ≤ third percentile, and 35% presented with growth ≤ 10th percentile. Among the 35% with GD, the most common form of GD was postnatal short stature (69.3%) (Table 5). GD manifested differently across the lifespan (Table 6).

Table 5. Profile of growth deficiency at birth and at the age of diagnosis

Growth measures	Total N	n	Valid %	n	Valid %
Gestational age < 37 weeks	1396	367	26.3	--	--
		≦ third		≦ 10th	
Birth length percentile	1170	90	7.6	164	14.0
Birth weight percentile	1387	79	5.7	213	15.4
Postnatal height percentile at diagnosis	1814	201	11.6	443	24.4
Postnatal weight percentile at diagnosis	1814	145	8.0	285	15.7
Height or weight percentile at birth or at diagnosis ≤ 10th percentile	1814	333	18.3	639	35.2
Growth ≤ 10th by age (years) at diagnosis		Height		Weight	
0.1–2.9	226	90	39.8	87	38.5
3.0–5.9	420	104	24.8	63	15.0
6.0–12.9	805	155	20.6	98	12.1
13.0–18.9	281	54	19.3	25	8.9
19.0–51.9	82	29	35.8	12	14.8
Among the 639 with height or weight ≦ 10th percentile at birth or at diagnosis		At birth		At diagnosis	
Proportion with height deficiency	639	164	38.2	443	69.3
Proportion with weight deficiency	639	213	41.4	285	44.6

While the majority of patients with height and/or weight deficiency presented with these deficiencies postnatally at the time of their diagnosis, 22% of subjects with height deficiency were only height-deficient at birth, and 39% of subjects with weight deficiency were only weight-deficient at birth.

The 4-Digit Code provides a more comprehensive view of the collective pattern and magnitude of GD across the population (Fig. 2). The height and weight ABC-Scores for this population document that height deficiency ≤ 10th percentile (ABC-Scores B and C) was more prevalent (29%) than weight deficiency (20%) (Fig. 2A1, 2A2). Nineteen percent of patients presented with growth ≤ third percentile (Growth Ranks 3 and 4: height and/or weight ≤ third percentile) and 33% presented with growth ≤ 10th percentile (Growth Ranks 2, 3 and 4: height and/or weight at or below the 10th percentile) (Fig. 2C). Height and weight percentiles were rarely concordant in an individual. Only one-third of the subjects presenting with growth deficiency had both height and weight moderately (ABC-Score = BB) or severely deficient (ABC-Score = CC) (Fig. 2B).

GD was as prevalent as the other core diagnostic features of FASD (i.e. FAS facial features and CNS abnormalities).

The prevalence of Rank 3 (11%) and Rank 4 (8%) GD (Fig. 1) was near-identical to the prevalence of Rank 3 (10%) and Rank 4 (9%) expressions of the FAS facial phenotype (Fig. 1). However, not everyone with Rank 3 or 4 facial phenotypes had Rank 3 or 4 GD. Only 37% (130/349) of those with Rank 3 or 4 GD (height and/or weight ≤ third percentile) had Rank 3 or 4 facial phenotypes, and only 38% (130/340) of those with Rank 3 or 4 facial phenotypes had Rank 3 or 4 GD. In contrast, 87% (305/349) with Rank 2, 3, or 4 GD (height or weight ≤ 10th percentile) had Rank 3 or 4 facial phenotypes. The prevalence of GD ≤ 10th percentile (Growth Ranks 2, 3 and 4) (33%) is equivalent to the prevalence of severe CNS structural/functional abnormalities (CNS Ranks 3 and 4) (39%) and the prevalence of severe CNS dysfunction (CNS Rank 3) (36%) among subjects who were 8 years of age and older (Fig. 1).

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Table 6. Discordance between height and weight deficiency ≤ 10th percentile at birth and age of diagnosis

Parameter	Total*	Growth-deficient subgroup**	N (% of total) % of growth-deficient subgroup		
	N	N	Height deficiency only	Weight deficiency only	Height and weight deficiency
At birth	1162	243	69 (5.9) 28	79 (6.8) 33	95 (8.2) 39
At diagnosis	1814	509	224 (12.3) 44	66 (3.6) 13	219 (12.1) 43
			GD at birth only	GD at diagnosis only	GD at birth and diagnosis
Height	1170	352	79 (6.8) 22	188 (16.1) 53	85 (7.3) 24
Weight	1387	351	136 (9.8) 39	138 (9.9) 39	77 (5.6) 22

*Total N reflects the number of subjects with data for both parameters being addressed in that row (e.g., At birth, 1,162 subjects had both height and weight data available at birth)

**The growth-deficient subgroup reflects the number of subjects with growth deficiency ≤ 10th percentile for each parameter being addressed in that row (e.g., at birth, 243 subjects had height and/or weight ≤ 10th percentile)

Growth profiles changed with age: height percentiles decreased and weight percentiles increased.

Among the 1162 patients with height and weight measures recorded in the FASDPN database at birth and at diagnosis, their mean birth weight percentile (48.0, SD = 31) was significantly lower than their mean birth length percentile (52.9, SD = 33) (paired T = 6.0, $P = 0.000$) (Fig. 3). Later in life, at the time of diagnosis, their mean weight percentile (51.0, SD = 32) was significantly higher than their mean height percentile (40.3, SD = 30) (paired T = –14.3, $P = 0.000$). Their mean weight percentile increased slightly but significantly by 3 percentage points after birth (paired T = 2.9, $P = 0.004$). In contrast, their mean height percentile decreased substantially (by 12.5 percentage points) and significantly after birth (paired T = –11.7, P = 0.000).

Growth patterns were comparable between females and males, with females being approximately 3–5 percentile points smaller in size. Of the 164 subjects with birth lengths ≤ 10th percentile, 52% had height percentiles later in life that were ≤ 10th percentile. Of the 174 subjects with birth weight ≤ 10th percentile, 37% had weight percentiles later in life that were ≤ 10th percentile.

Although FAS is defined by GD at any time across the lifespan (birth through adulthood), the 4-Digit Code Growth Rank was based on birth measures only 18% (324/1814) of the time.

FASD diagnostic guidelines, including the 4-Digit Code, allow prenatal and/or postnatal evidence of GD to meet criterion for FAS. It is important to note that when ranking growth using the 4-Digit Code, the clinician first separates the growth curve into two parts: 1) prenatal growth, i.e. birth measures; and 2) postnatal growth, i.e. all measures subsequent to birth (infancy through adulthood). Growth is then ranked based on the part of the growth curve presenting with the lowest height percentile. The 4-Digit Code emphasizes height deficiency; this is because weight gain and loss is more easily influenced by other risk factors such as nutrition and illness. Using this more prescribed approach, we queried how often the Growth Rank was derived from birth measures, and how often the birth length percentile was lower than all height percentiles measured later in life (infancy through adulthood).

Within our cohort, 1163 (64%) patients had both their birth lengths and birth weights recorded. The 4-Digit Code allows only height and weight measures taken on the same day to be used to rank growth. Of the

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1163 subjects, only 324 (28%) had their Growth Rank derived from birth measures. In other words, only 28% had a birth length percentile that was lower than all subsequent height percentiles measured later in life. Not all of these 324 subjects were GD at ≤ 10th percentile: Rank 4, N = 22 (7%); Rank 3, N = 39 (12%); Rank 2, N = 47 (15%); and Rank 1, N = 216 (67%). Across the entire cohort of 1814 subjects, Growth Rank was derived from birth measures in only 18% of patients (324/1814). This finding is key to addressing our next question: is GD correlated with PAE in this clinical population?

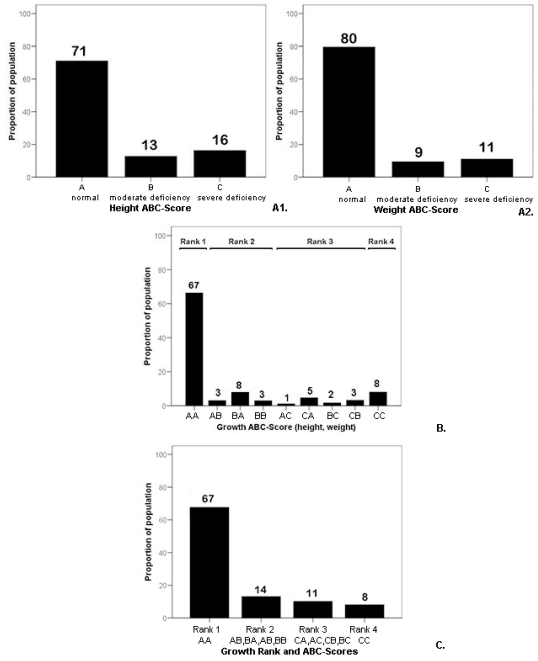

Figure 2. Prevalence and pattern of growth deficiency among 1814 subjects

A) Prevalence of 4-Digit Code height ABC-Score and weight ABC-Score (A = > 10th percentile, B = >third and ≤ 10th percentile; C = ≤ third percentile.). B) Prevalence of 4-Digit Code Growth ABC-Scores (the two letters reflect the height and weight ABC-Scores respectively). C) Prevalence of the 4-Digit Code Growth Ranks.

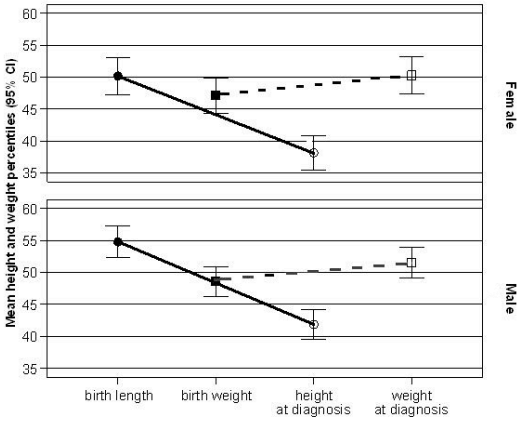

Figure 3. Growth profiles changed with age: height percentiles decreased and weight percentiles increased

Among 1162 patients with height and weight measures at birth and later in life at the time of diagnosis, paired analyses documented the mean weight percentile (dotted line) increased slightly, but significantly with age. The mean height percentile decreased substantially with age (solid line). At birth, mean weight was significantly lower than mean length. Later in life, at the time of diagnosis, mean height was significantly lower than mean weight. Growth patterns were comparable between females and males with females roughly 3–5 percentile points smaller in size. CI, confidence interval.

Correlation between PAE and GD

Growth deficiency, as uniquely ranked by the 4-Digit Code, was significantly correlated with PAE after controlling for other risk factors, including prenatal tobacco exposure.

The mean number of days per week of alcohol exposure during pregnancy increased linearly and significantly with increased GD Rank (Fig. 4A). The prevalence of prenatal exposure to tobacco was high (86–91%), but did not vary significantly with Growth Rank (Fig. 4B). Smoking status was available for 63% of the population. Growth Rank in this clinical population of 1,814 patients was derived from birth measures only 18% of the time, thus smoking status had very little impact on the correlation detected in Fig. 4A between alcohol exposure and the 4-Digit Code Growth Rank.

Since the analyses above document that the 4-Digit Code Growth Rank was based on postnatal growth measures 82% of the time, we looked at other

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postnatal risk factors (physical/sexual abuse, foster care placement) that may impair childhood growth. The prevalence of these individual factors did not increase with increasing Growth deficiency Rank (Fig. 4B.). To the contrary, the prevalence of physical/sexual abuse and out-of-home placement was lowest among those with the most severe GD (Growth Rank 4).

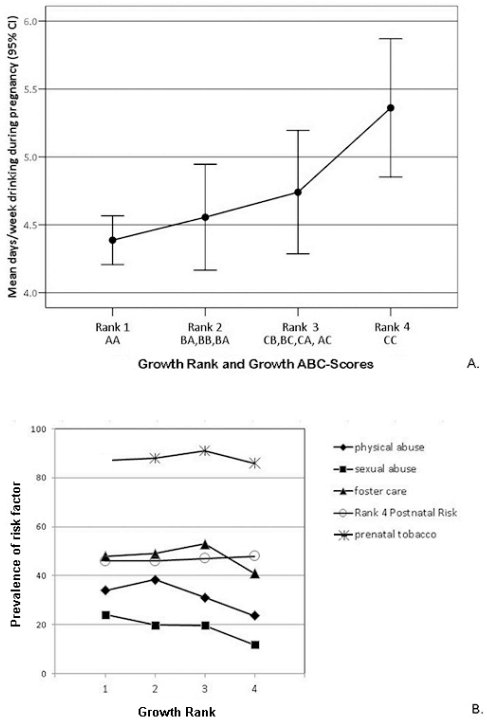

Figure 4. Growth deficiency was significantly correlated with PAE after control for other risk factors including tobacco

A) The mean number of days per week of drinking during pregnancy increased linearly with increased growth deficiency measured by Growth Rank (n = 968, one-way ANOVA: F = 4.5, P = 0.004, linear F = 12.4 P = 0.000). Error bars reflect 95% confidence intervals. The Growth ABC-Scores are defined in Tables 2 and 3. B) The prevalence of prenatal exposure to tobacco was high (86–91%), but did not vary significantly with Growth Rank. The prevalence of other postnatal risk factors that may impair growth (trauma, foster placement) did not increase with increasing Growth Rank.

Finally, the 4-Digit Code generates a composite measure of postnatal risk for each patient, called the Postnatal Risk Rank, that documents the number and severity of all adverse postnatal conditions the patient experienced on a 4-point scale (1= no risk, 2 = unknown risk, 3 = some risk, 4 = high risk).

The prevalence of patients experiencing the highest level of overall postnatal risk (Rank 4) did not vary across the four Growth Ranks (Fig. 4B).

PAE was significantly correlated with preterm birth (< 37 weeks of gestation) and postnatal short stature (height ≤ 10th percentile).

Univariate analyses document that mean percentiles for birth length, birth weight, and height at diagnosis were significantly lower among subjects with PAE across all three trimesters than among subjects with PAE only in the first trimester (T = 2.1, P = 0.04; T = 2.3, P = 0.02; T = 2.2, P = 0.03, respectively) (Fig. 5A). Mean gestational age was marginally, but significantly lower among subjects with three trimesters of alcohol exposure (37.9 weeks, SD = 3.2) compared to subjects with exposure in just the first trimester (37.3 weeks, SD = 3.5) (T = 2.2, P = 0.03) (Fig. 5A). Clinically, the prevalence of preterm delivery (< 37 weeks of gestation) increased with increasing trimesters of exposure (first trimester only, 20%; first and second trimesters only, 23%; all three trimesters, 28%) (Chi^2 linear trend = 6.7, P = 0.01). Logistic regression documented that subjects with alcohol exposure across all three trimesters were at a 1.6-fold increased risk (95% CI 1.1–2.5) of postnatal short stature relative to subjects with alcohol exposure only in the first trimester. Prenatal tobacco exposure was not significantly associated with any postnatal growth outcomes (Fig. 5B) and did not attenuate the risk of postnatal short stature associated with PAE in the logistic regression analysis.

Prenatal tobacco exposure was significantly correlated with low birth weight.

Mean birth length percentile was significantly lower (53.2, SD = 33.5) among those with prenatal tobacco exposure than among those without prenatal tobacco exposure (64.4, SD = 32.0; T = 2.9, P = 0.004) (Fig.

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5B). Mean birth weight percentile was also significantly lower (48.1, SD = 31.2) among those with prenatal tobacco exposure than among those without prenatal tobacco exposure (55.2, SD = 31.0; T = 2.2, *P* = 0.03).

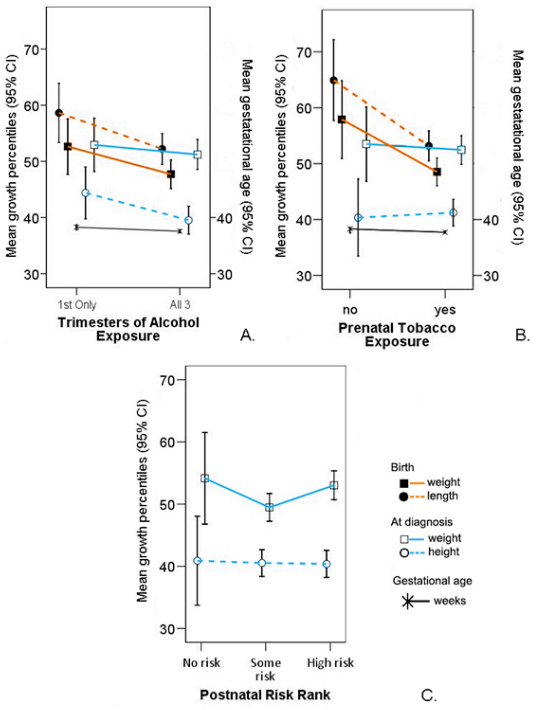

Figure 5. Prenatal alcohol exposure was significantly correlated with preterm birth and postnatal short stature

A) Mean percentiles for birth length, birth weight, and height at diagnosis were significantly lower among subjects with prenatal alcohol exposure all three trimesters compared to just the first trimester (T = 2.1, P = 0.04; T = 2.3, P = 0.02; T = 2.2, P = 0.03 respectively). B) Prenatal tobacco exposure was correlated with a significant reduction in prenatal, but not postnatal growth measures (birth length T = 2.9, P = 0.004; birth weight T = 2.2, P = 0.03). Growth Rank in this study sample of 1814 patients was derived from birth measures only 2.9% of the time, thus smoking status had very little impact on the correlation detected in Fig. 4A between alcohol exposure and the 4-Digit Code Growth Rank in our population. Mean gestational age in weeks was marginally, but significantly lower among those with three trimesters of alcohol exposure (37.9 weeks, SD = 3.2) compared to those with exposure in just the first trimester (37.3 weeks, SD = 3.5) (T = 2.2, P = 0.03). Mean gestational age was comparable between smokers and nonsmokers. C). Postnatal growth (mean height and weight percentiles at the time of diagnosis) did not vary significantly with increasing Postnatal Risk Rank, as defined by the 4-Digit Code.

Mean gestational age was comparable between those with (37.4 weeks, SD = 3.1) and without (37.6 weeks, SD = 3.9) prenatal tobacco exposure (Fig. 5B). Logistic regression documented that subjects with exposure to prenatal tobacco were at a 2.1-fold increased risk (95% CI 1.1–4.3) for birth weight ≤ 10th percentile relative to subjects with no tobacco exposure. Prenatal alcohol exposure did not attenuate this risk or further contribute to the risk for low birth weight.

Other postnatal risks (trauma, foster placement) were not associated with postnatal growth deficiency.

Postnatal growth (mean height and weight percentiles at the time of diagnosis) did not vary significantly with increasing Postnatal Risk Rank (1, no risk; 2, unknown risk; 3, some risk; 4, high risk) (Fig. 5C).

Growth deficiency was highly correlated with, and predictive of, CNS dysfunction

Growth deficiency was as highly correlated with severe CNS dysfunction as the FAS facial phenotype.

Among patients old enough to engage in comprehensive neuropsychological assessments (8 years of age and older), the prevalence of severe CNS dysfunction (CNS Rank 3) increased significantly and linearly with increasing GD as measured by the Growth Rank (Fig. 6A1). Mean Full Scale IQ was significantly lower among patients with moderate to severe GD (Ranks 3 and 4) compared to patients with normal or mild GD (Ranks 1 and 2) (Fig. 6A2). The correlations between growth deficiency and CNS dysfunction were near identical to the correlations between the FAS facial phenotype and CNS dysfunction (Fig. 6B1, 6B2).

GD occurs across the full spectrum of FASD diagnoses (FAS, PFAS, SE/AE and ND/AE). The more severe the diagnosis, the more prevalent and severe the GD.

All measures of growth (mean height and weight percentiles at birth and at the age of diagnosis) decreased linearly and significantly with increasing severity of FASD diagnosis (Fig. 7A). This was also

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reflected in the Growth Rank. The prevalence of GD (Growth Ranks 2, 3 and 4) increased linearly with increasing severity of FASD diagnosis (Fig. 7B).

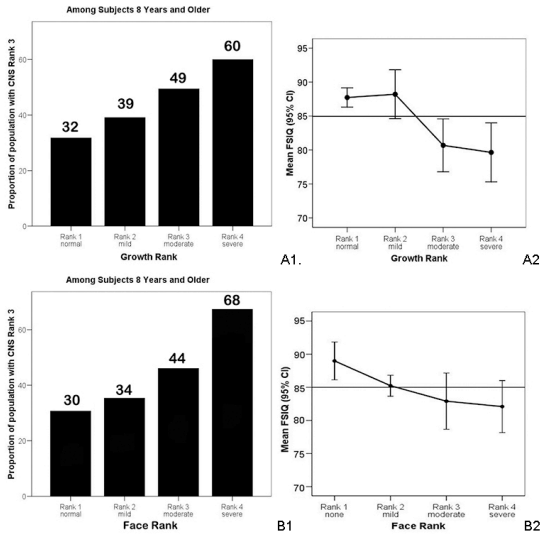

Figure 6. The correlation between growth deficiency and central nervous system (CNS) dysfunction was as strong as the correlation between the FAS facial phenotype and CNS dysfunction

A1). The prevalence of severe CNS dysfunction (CNS Rank 3) increased significantly with increasing Growth Rank among those aged 8 years and older at the time of diagnosis (i.e. those old enough to have CNS function assessed) (N = 871: Chi2 linear-by-linear association = 24.8, P = 0.000). A2) The mean FSIQ among subjects with Rank 3 or 4 growth deficiency was significantly lower than among subjects with Growth Ranks 1 or 2 (one-way ANOVA: F = 7.2, P = 0.000: SNK: Ranks 3, 4 < Ranks 1, 2). B1) The prevalence of severe CNS dysfunction (CNS Rank 3) increased significantly with increasing Growth Rank among those aged 8 years and older at the time of (N = 871: Chi2 linear-by-linear association = 24.8, P = 0.000). B2) The mean FSIQ among subjects with Rank 3 or 4 FAS facial phenotypes were significantly lower than among subjects with Rank 1 or 2 facial phenotypes (one-way ANOVA: F = 3.5, P = 0.02: SNK: Ranks 3,4 < Ranks 1,2).Chi2, Chi square test; CI, confidence interval; CNS, central nervous system; FSIQ, full scale intelligence quotient; SNK Student–Newman–Keuls test.

FAS has the lowest mean growth percentiles and the highest prevalence of GD (100%) because GD is required for a diagnosis of FAS, but the PFAS, SEAE, and NDAE diagnostic criteria do not require GD (height and/or weight ≤ 10th percentile). Nevertheless, even those with just moderate CNS dysfunction (ND/AE) presented with GD ≤ 10th percentile, albeit only half as often (24%) as those with PFAS (46%). Thus, the significant reduction in mean height and weight percentiles at birth and at the age of diagnosis with increasing severity of diagnosis (ND/AE, SE/AE and PFAS) further illustrates the correlation between growth and CNS impairment across the full spectrum of FASD.

Intercorrelation and concordance of GD, the FAS facial phenotype, and microcephaly

GD is highly correlated with the FAS facial phenotype and microcephaly, but not every patient with the FAS facial phenotype and/or microcephaly has GD.

The three core physical features of FASD are GD, the FAS facial phenotype, and microcephaly.

Although the presence of these features is highly intercorrelated, they are not 100% concordant within each patient. Patients do not present with all or none of these physical features (Table 7). For example, GD ≤ 10th percentile (Ranks 2–4) was present in 26% (n = 382) of 1470 subjects who did not present with the FAS facial phenotype (Rank 4) or microcephaly (occipital–frontal circumference [OFC] ≤ third percentile). Documentation of GD Rank 2, 3, or 4 in their FASD 4-Digit Code alerts clinicians that these 382 subjects are at a two-fold increased risk for severe CNS dysfunction, despite absence of the FAS facial phenotype and microcephaly. Almost half will present with severe CNS dysfunction later in childhood. Among the 172 patients who were old enough to fully assess CNS function (≥ 8 years old), 42% presented with severe CNS dysfunction (CNS Rank 3).

GD and the FAS facial phenotype

GD is highly correlated, but not highly concordant with the FAS facial phenotype.

Mean height and weight percentiles at birth and at the age of diagnosis decreased significantly with increasing severity of the FAS facial features Rank (Fig. 8A).

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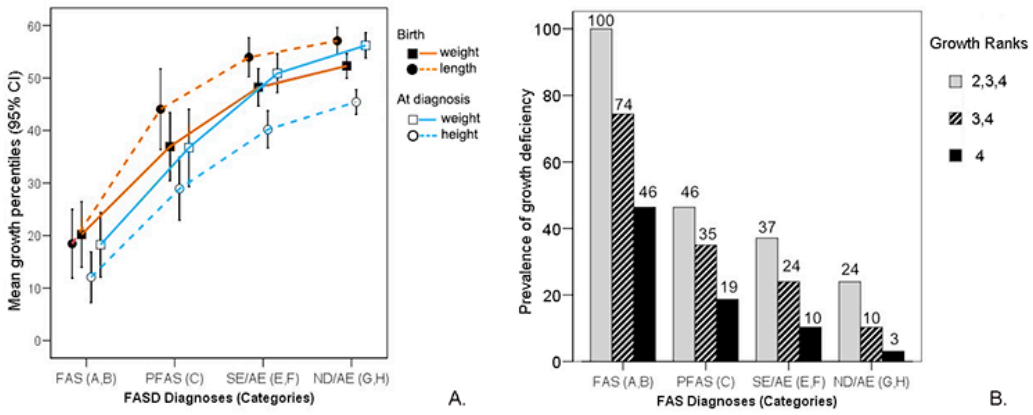

Figure 7. The more severe the FASD diagnosis, the more prevalent and severe the growth deficiency

A) Growth deficiency occurs across the full spectrum of FASD diagnoses (FAS, PFAS, SE/AE and ND/AE). All measures of growth (height and weight percentiles at birth and at the age at diagnosis) decreased significantly with increasing severity of FASD diagnosis (one-way ANOVA linear terms: F = 78.8, 72.0, 111.5, and 120.1 respectively; all P = 0.000). B) Clinically, the prevalence of patients with Growth deficiency Ranks 2, 3 and/or 4 increased significantly with increasing severity of FASD diagnosis (Chi2 linear-by-linear = 179, P = 0.000). The gray bars reflect individuals with height or weight < the 10th percentile. Striped bars reflect individuals with height or weight < third percentile. The black bars reflect individuals with height and weight < third percentile. CI, confidence interval; PFAS, partial FAS; SE/AE, static encephalopathy/alcohol-exposed; ND/AE, neurobehavioral disorder/alcohol-exposed.

Clinically, the proportion of patients with one, two, or all three of the FAS facial features increased significantly and linearly with increasing GD Rank (Fig. 8B).

Despite these significant correlations, most (83%) patients with GD (Growth Ranks 2, 3 and 4; N = 603) did not present with the Rank 4 FAS facial phenotype (N = 502) (Table 7). Since GD is a major predictor of severe CNS dysfunction in this population, excluding GD as a FASD diagnostic criteria would prevent clinicians from identifying those infants/toddlers under the age of 8 years who are at a two-fold increased risk for severe CNS dysfunction; dysfunction that will not be detectable until later in childhood. In our population, 44% (93/213) of children aged 8 years and older who presented with GD (Ranks 2–4), but not the Rank 4 FAS facial phenotype, had severe CNS dysfunction (CNS Rank 3).

GD and microcephaly

GD is highly correlated, but not highly concordant, with microcephaly.

The OFC percentile decreased significantly with decreasing birth length, birth weight, height at diagnosis, and weight at diagnosis percentiles (Pearson correlation coefficients: 0.33, 0.37, 0.42, and 0.52, respectively; all *P*-values = 0.000). Mean OFC decreased significantly and linearly with increased Growth Rank (one-way ANOVA, F = 311, *P* = .000) (Fig. 9A). Individuals with severe GD (Rank 4) had a mean OFC percentile of 11.6 (SD = 15) compared to 51.7 (SD = 27) among individuals with normal growth (Rank 1). Clinically, the prevalence of microcephaly (OFC ≦ third percentile) increased significantly and linearly with increased Growth Rank (Chi^2 linear-by-linear association = 309, *P* = 0.000) (Fig. 9B).

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Table 7. Cross-tabulation of Face Rank, Growth Rank, and microcephaly among 1814 patients with prenatal alcohol exposure

Face Rank			Microcephaly: OFC ≤ third Percentile		Total
			No: n	Yes: n (row %)	
1 none	Growth Rank	1: normal	406	12 (3)	418
		2: mild	49	5 (3)	54
		3: moderate	30	5 (14)	35
		4: severe	8	1 (11)	9
		Total	495	21 (4)	516
2 mild	Growth Rank	1: normal	597	44 (7)	641
		2: mild	127	16 (11)	143
		3: moderate	84	27 (24)	111
		4: severe	30	32 (52)	62
		Total	839	118 (12)	957
3 moderate	Growth Rank	1: normal	84	7 (8)	91
		2: mild	23	5 (18)	28
		3: moderate	15	12 (44)	27
		4: severe	14	19 (58)	33
		Total	136	43 (24)	179
4 severe	Growth Rank	1: normal	57	4 (7)	61
		2: mild	18	12 (40)	30
		3: moderate	16	13 (45)	29
		4: severe	12	30 (71)	42
		Total	103	59 (36)	162
Grand total			1570	244 (13)	1814

*Correlations between Growth Ranks, Face Ranks, and presence of microcephaly: growth and face, $Chi^2 = 185.8$, $P = 0.0$; growth and microcephaly: $Chi^2 = 327.3$, $P = 0.0$; face and microcephaly: $Chi^2 = 132.0$, $P = 0.000$

Despite these significant correlations, most (71%) patients with GD (N = 603) did not have microcephaly (N = 426) (Table 7). Thirteen percent of the entire study population (244/1814) had microcephaly (OFC $\leq$ 3rd percentile). The distribution of Growth Ranks among these 244 subjects was: Rank 4 (34%), Rank 3 (23%), Rank 2 (16%), and Rank 1 (27%).

In contrast, 33% of the study population (603/1814) had GD (Growth Ranks 2, 3, or 4), and only 29% of those with GD (177/603) had microcephaly. Again, since GD is a major predictor of severe CNS dysfunction in this population, exclusion of GD as a FASD diagnostic criterion would prevent clinicians from identifying the infants/toddlers under 8 years of age that are at two-fold increased risk for severe CNS dysfunction; dysfunction that will not be detectable until later in childhood. In our population, 45% (86/192) of children aged 8 years or older who presented with GD (Ranks 2-4), but no microcephaly, had severe CNS dysfunction (Rank 3). Furthermore, 42% (72/171) of children aged 8 years or older who presented with GD (Ranks 2-4), but no microcephaly or Rank 4 FAS facial phenotype, had severe CNS dysfunction (Rank 3). Microcephaly and the FAS facial phenotype may be highly correlated with GD, but they cannot be used in lieu of growth measures to identify all infant/toddlers at risk for severe CNS dysfunction.

Can GD be used to predict which infants and toddlers will present with severe CNS dysfunction later in childhood when they are old enough to assess brain function?

Individuals with Growth Ranks 3 or 4 were twice as likely to present with severe CNS dysfunction than individuals with no GD.

Logistic regression analyses provided evidence that individuals with Growth Ranks 3 and 4 were at significantly greater risk for severe CNS dysfunction (CNS Rank 3) than individuals with normal growth (Rank 1) (Table 8). This risk was even higher for individuals presenting with FAS facial phenotypes at Ranks 3 or 4. Among 735 patients aged 9 years or older, and compared to patients with normal growth (Rank 1), those with Growth Rank 4 had a 1.96-fold greater risk of having CNS Rank 3, and patients with Growth Rank 3 had a 1.8-fold increased risk of having CNS Rank 3.

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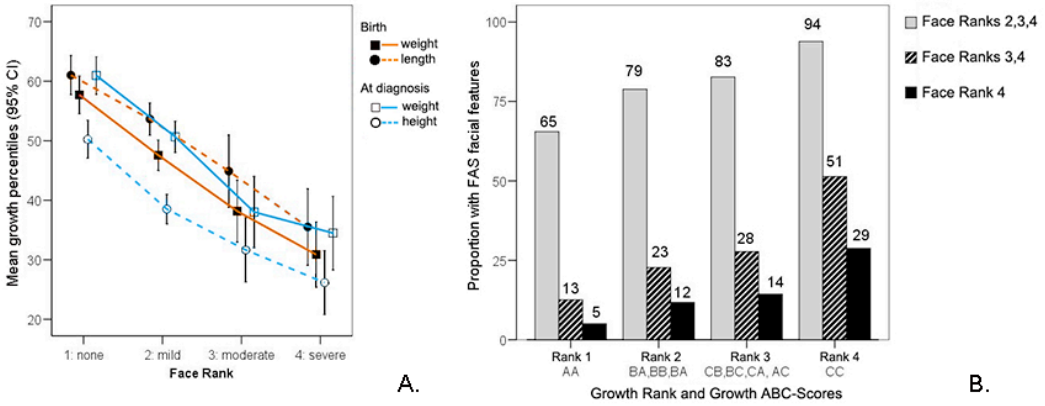

Figure 8. The more severe the growth deficiency, the more severe the FAS facial phenotype

A) Mean height and weight percentiles at birth, and at the age of diagnosis, decrease significantly with increasing severity of the FAS facial phenotype, (one-way ANOVA: birth length, F = 21.4; P = 0.000; birth weight, F = 30.3, P = 0.000; height at diagnosis, F = 36.8, P = 0.000; weight at diagnosis, F = 35.6; P = 0.000). B) Clinically, the proportion of patients with one, two or all three of the FAS facial features increased with increasing Growth deficiency Rank. (Chi2 linear-by-linear = 171, P = 0.000). . Gray bars reflect individuals with 1 to all 3 of the FAS facial features. Striped bars reflect individuals with 2.5 to all 3 facial features. Black bars reflect individuals with all 3 of the FAS facial features. CI, confidence interval.

Compared to patients with normal facial features (Rank 1), those with the full FAS facial phenotype (Rank 4) had a 3.8-fold increased risk of having CNS Rank 3, and patients with Face Rank 3 had a 1.9-fold increased risk of having CNS Rank 3.

Infants/toddlers with GD were twice as likely to have severe CNS dysfunction upon re-evaluation later in childhood.

Although most patients evaluated in the FASDPN clinic are seen only once, 46 subjects received a second diagnostic evaluation because they were too young (≦ 8 years of age) at their first evaluation to engage in the comprehensive neurocognitive assessment required to confirm or rule out severe CNS dysfunction (CNS Rank 3) (Table 9).

Data from these subjects allowed longitudinal assessment of how well GD (and the FAS facial features) predicted which toddlers/infants would present with severe CNS dysfunction (CNS Rank 3) upon re-evaluation later in childhood when they were old enough to engage in more comprehensive neurocognitive assessments. The 46 children were, on average, 4.3 years old (SD = 2.1) at their first evaluation, and 10.3 years old (SD = 3.4) at their second evaluation. Their gender, racial, and FASD diagnostic profiles matched that of the entire study population. GD and FAS facial features were highly predictive of who would present with severe CNS dysfunction (CNS Rank 3) later in childhood (Table 9).

These outcomes are consistent with the logistic regression outcomes described above. Seventy percent of infants/toddlers with Growth Ranks 2, 3, or 4 (9/13) received a CNS Rank 3 upon re-evaluation later in childhood. Only 46% (15/33) with Growth Rank 1 received a CNS Rank 3 upon re-evaluation. Risk of severe CNS dysfunction appeared to increase linearly with increasing severity of GD. Sixty-five percent of those with Face Ranks 2, 3 or 4 (22/34) received a CNS Rank 3 upon re-evaluation. Only 17% (2/12) with Face Rank 1 received a CNS Rank 3 upon re-evaluation (Fisher exact $P < 0.05$). Those with microcephaly were also at increased risk for severe CNS dysfunction.

Eighty percent of those with microcephaly received a CNS Rank 3 upon re-evaluation.

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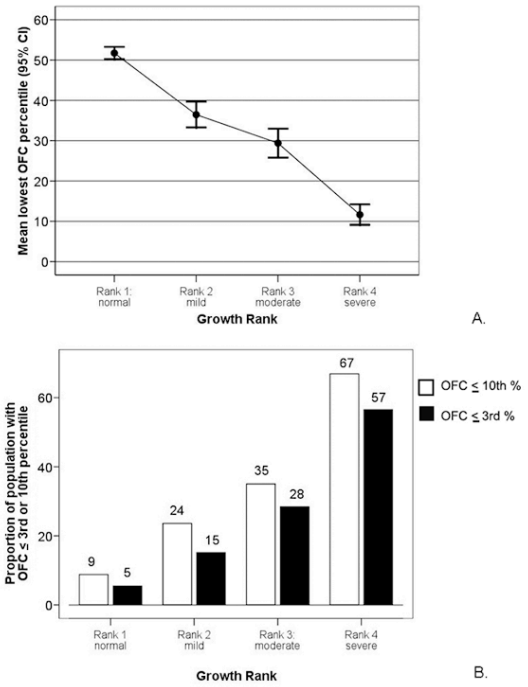

Figure 9. The more severe the growth deficiency, the smaller the head circumference

A) The mean OFC percentile decreased significantly and linearly with increasing Growth deficiency Rank. B) Clinically, the proportion of subjects with an OFC ≤ third percentile (black bars) or ≤ 10th percentile (white bars) increased significantly with increasing Growth deficiency Rank). CI, confidence interval; OFC, occipital–frontal circumference.

Only 49% of those with normal head circumferences received a CNS Rank 3 upon re-evaluation.

Does the risk of severe CNS dysfunction (Rank 3) increase when a patient presents with one, two, or all three of the sentinel physical features of FASD (GD, FAS facial features, and microcephaly)?

With the addition of each sentinel physical feature (GD; GD + FAS facial features; GD + FAS facial features + microcephaly) the prevalence of severe CNS dysfunction increased significantly from 41% to 56% to 67%.

Table 8. Individuals with growth deficiency or facial features were over 2-fold more likely to have severe CNS dysfunction†

	Frequency		Unadjusted		Adjusted for Face or Growth	
	N	CNS Rank 3* n (%)	OR	95% CI	OR	95% CI
Growth Rank						
1	517	162 (31%)	Referent 1.0			
2	96	36 (38%)	1.32	0.84–2.07	1.25	0.79–1.98
3	79	39 (49%)	2.14	1.32–3.45	1.77	1.07–2.91
4	43	24 (56%)	2.77	1.47–5.20	1.96 **	1.01–3.81
Face Rank						
1	182	52 (29%)	Referent 1.0			
2	439	144 (33%)	1.22	0.84–1.78	1.12	0.76–1.64
3	55	26 (47%)	2.24	1.21–4.16	1.93	1.03–3.63
4	59	39 (66%)	4.88	2.60–9.13	3.82	1.98–7.33

†Odds Ratio (OR) and 95% confidence intervals for the association between the 4-Digit Code Face and Growth Ranks and severe CNS dysfunction (CNS Rank 3) among 735 patients 9 years of age or older (old enough to accurately assess CNS function).

*CNS Rank 3 is defined by 3 or more domains of brain function, 2 or more SDs below the mean.

**Explanation: The odds of CNS rank 3 for a patient with Rank 4 growth are 1.96 times the odds of CNS Rank 3 for a patient with Rank 1 growth, all other things being equal. 95% confidence intervals that do not include 1.00 are statistically significant at $p < 0.05$.

The prevalence of severe CNS dysfunction (CNS Rank 3) increased significantly among subjects who presented with one or more of the sentinel physical features of FAS (GD, FAS facial features, and/or microcephaly) (Table 10). Prevalence of CNS Rank 3 increased with increasing magnitude of GD and increased number of sentinel physical features. The data shown in Table 8 are from children aged 8 years and older – these children were deemed old enough to engage in a sufficient level of functional assessment to confirm or rule out a CNS Rank 3 classification.

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Table 9. Infants/toddlers with sentinel physical features were most at risk for severe CNS dysfunction later in childhood†

Sentinel physical feature	CNS Rank increased to Rank 3 at the second diagnostic evaluation	
	No n (%)	Yes n (%)
Growth Rank at first evaluation*		
1 (normal)	18 (54)	15 (46)
2 (mild)	3 (43)	4 (57)
3 (moderate)	1 (33)	2 (67)
4 (severe)	0 (0)	3 (100)
Face Rank at first evaluation**		
1 (normal)	10 (83)	2 (17)
2 (mild)	7 (39)	11 (61)
3 (moderate)	2 (33)	4 (67)
4 (severe)	3 (30)	7 (70)
Microcephaly at first evaluation ***		
Normal OFC	21 (51)	20 (49)
Microcephaly	1 (20)	4 (80)

†Among 46 subjects with two evaluations when they were on average 4 and 10 years of age, respectively, those with growth deficiency, FAS facial features, or microcephaly at the first diagnostic evaluation were more likely to present with severe CNS dysfunction (CNS Rank 3) at their second diagnostic evaluation.

*Chi^2 linear-by-linear association 3.7; $P < 0.05$. ** Fisher exact for Rank 1 vs Ranks 2,3,4 $P < 0.05$. *** Fisher's Exact Test $P = 0.20$

OFC, occipital–frontal circumference

A CNS Rank 3 requires 3 or more domains of function (e.g., intellect, executive function, language, memory, etc) to be two or more standard deviations below the mean on standardized tests administered by professional clinicians. Severe CNS dysfunction occurred in 30% of patients with none of the sentinel physical features. With the addition of each sentinel physical feature (GD $\leq 10^{th}$ percentile [Ranks 2, 3 and 4], FAS facial features [Ranks 3 and 4], and microcephaly $\leq$ third percentile), the prevalence of severe CNS dysfunction increased significantly from 41% to 56% to 67%, respectively.

Table 10. Prevalence of severe CNS dysfunction among 854 subjects† that presented with sentinel physical features

Sentinel physical feature(s) present	Proportion with CNS Rank 3: severe dysfunction			
	Growth Ranks 2,3,4 Height and/or weight $\leq 10^{th}$ %		Growth Ranks 3,4 Height and/or weight $\leq 3\%$	
	%	n	%	n
None	30	153/514	31	182/594
Growth deficiency only	41*	63/153	47*	34/73
Growth and face	56*	20/36	68*	13/19
Growth, face, and microcephaly	67*	18/27	68*	17/25

† Subjects are 8 years of age and older presenting with one or more sentinel physical features of FASD

* Chi^2, $P < 0.05$ when compared to prevalence of CNS Rank 3 when no features present

Microcephaly is occipital–frontal circumference (OFC) ≤ third percentile. Face includes Face Ranks 3 and 4. Growth reflects the definitions in the two column headings

Discussion

Since the discovery of FAS in 1973 [1,2,6,7], GD has been a core diagnostic feature of FASD [3–5,19]. Based on the findings of this study (see Appendix), and near identical findings published by Carter et al. [20], we recommend that GD should remain a core diagnostic feature of FASD.

GD is caused by PAE

Laboratory studies have unequivocally confirmed that PAE causes prenatal and postnatal GD [8,10,11]. However, attributing the extent of GD that is caused by PAE in a clinical population is challenging because of the multitude of other prenatal and postnatal adverse exposures and events that also contribute to GD, such as prenatal tobacco exposure, trauma, and neglect [19,21]. Nevertheless, in our population, postnatal short stature was the most prevalent form of GD in our clinical population, and

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was significantly correlated with PAE after controlling for these other risk factors.

Our findings are remarkably consistent with the literature, both past and present. For example, as far back as 1998, Habbick et al. [22] concluded, "*despite retarded bone age readings, children with FAS do not show significant catch-up growth in height, although they do show relative gain in weight. Short stature can be used as a diagnostic criterion in individuals with FAS beyond childhood, whereas thinness is a less reliable feature.*" More recently, in a review of growth among children prenatally exposed to drugs, Nordstrom-Klee et al. [12] report that while growth deficits caused solely by prenatal cigarette exposure are unlikely to persist beyond infancy, the effects of prenatal exposure to alcohol on growth continue well into childhood. In one study, Greene et al. [23] found PAE to negatively affect average preschool height, but not weight. This difference persisted after controlling for the use of other substances and background factors. Carter et al. [20] recently reported that, among children with heavy PAE, "*children born small for gestational age (SGA) with postnatal growth restriction (height ≦ 10th percentile) were most heavily exposed. Exposure was intermediate for those born SGA with catch-up growth and lowest for those without prenatal or postnatal growth restriction. Effects on neurocognition were strongest in children with both prenatal and long-term growth restriction, more moderate in those with fetal growth restriction and postnatal catch-up, and weakest in those without growth restriction*".

The strong correlation between GD and the FAS facial features in our study provide further support that PAE is contributing to the GD observed in our clinical population. It is well understood that GD is not specific to (caused only by) PAE, but the FAS facial phenotype is. The fact that GD correlates with both the FAS Facial Rank and PAE leaves little doubt that PAE is contributing to GD in our clinical population.

GD is prevalent

Second, GD is not a rare outcome among individuals with PAE. In fact, it occurred in 33% of our clinical population and was as prevalent as the other core diagnostic features of FASD (the FAS facial features and severe CNS dysfunction). GD also occurred across the full spectrum of FASD, not just among those with full FAS. Over the decades, clinicians, including us, have questioned whether GD should ever have been included as a diagnostic criterion, since the small group of children from whom the term FAS was coined in 1973 came from a failure-to-thrive clinic [2,6,7]. Clearly, they all had GD; but were they a representative sample of all individuals with FAS? The results of our study affirm that they were. Individuals with PAE who present with GD and the FAS facial phenotype present with the most severe CNS dysfunction. In our clinical population, 92% of patients with GD and the FAS facial phenotype also presented with severe CNS abnormalities and met the criteria for FAS. As the prevalence and severity of GD decreases, so does the prevalence and severity of the FAS facial features and CNS dysfunction. The result is a spectrum of FASD diagnoses that correlate linearly with the spectrum of GD (FAS: 100% GD; PFAS: 46% GD; SE/AE: 37% GD; ND/AE: 24% GD).

GD is highly correlated with, and predictive of, CNS dysfunction

Finally, and perhaps of greatest clinical importance, GD is highly correlated with and predictive of CNS dysfunction. Many studies have documented the correlation between GD – especially short stature – and cognitive/behavioral dysfunction [24,25]. In our clinical population with PAE, we too found highly significant linear correlations between GD (especially postnatal short stature) and CNS dysfunction – this finding is especially important when evaluating infants and toddlers with PAE. Most children with cognitive or other developmental challenges caused by PAE do not fully exhibit these challenges until they reach school-age. For example, half of the children in our clinical population diagnosed with full FAS had normal Bayley developmental scores as infants; thus, it would be a mistake to interpret their early normal development as evidence that PAE caused no harm. Although infants and toddlers are too young to engage in a comprehensive assessment of brain function, their growth and facial features are

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easily measured. This study has confirmed that GD is as powerful a predictor of severe CNS dysfunction as the FAS facial features. Infants and toddlers with PAE, normal early development, and Rank 3 or 4 GD were two to three-fold more likely to present with severe CNS dysfunction later in childhood than those without GD. Those with Rank 3 or 4 FAS facial phenotypes were two to five-fold more likely to present with severe CNS dysfunction. Those with both GD and the FAS facial features were almost assured of presenting with severe CNS dysfunction later in childhood. GD is an indispensable tool for the early identification of infants/toddlers at the highest risk for severe CNS dysfunction. Infants and toddlers with PAE who present with GD and/or the FAS facial phenotype should be referred to, and should qualify for, early intervention to mitigate this risk.

Conclusions

The outcomes of this study empirically confirm and illustrate the role of GD in the diagnosis of, and early intervention for, FASD. We will continue to include GD as a core diagnostic feature of FASD in the 4-Digit Code for the following reasons:

1. Laboratory studies confirm PAE causes GD. The 4-Digit Code Growth Rank documents GD attributable to PAE.
2. GD is not only prevalent across the full spectrum of FASD; it is as prevalent as the other core diagnostic features (e.g., the FAS facial features and CNS abnormalities).
3. GD is not only highly correlated with severe CNS dysfunction, but is highly predictive of severe CNS dysfunction. In fact, GD is so highly predictive of severe CNS dysfunction, it should be used to identify those infants/toddlers with PAE who are at high risk for severe CNS dysfunction, and qualify them for early intervention services – despite apparently normal early development.

Appendix. Summary of key findings

1. GD is as prevalent as the other core diagnostic features of FASD (the FAS facial features and CNS abnormalities).
    a. 19% had GD $\leqq$ third percentile (Growth Ranks 3 and 4)
        - 19% had the FAS facial features (Face Ranks 3, 4)
        - 18% had CNS structural/neurological abnormalities (CNS Rank 4)
    b. 33% had GD $\leqq 10^{th}$ percentile (Growth Ranks 2, 3 and 4)
        - 36% had severe CNS dysfunction (CNS Rank 3)
2. GD $\leqq 10^{th}$ percentile occurs across the full spectrum of FASD diagnoses and increases significantly in prevalence with increasing severity of diagnosis (ND/AE 24%; SE/AE 37%; PFAS 46%; FAS 100%).
3. The profile of GD changes with age, with the most prevalent form being postnatal short stature.
    a. Weight is more deficient (by 5 percentile points) than length at birth.
    b. Height is more deficient (by 11 percentile points) than weight later in life (infancy to adulthood).
    c. The mean weight percentile increases slightly and significantly (by 3 percentage points) with age.
    d. The mean height percentile decreases substantially and significantly (by 13 percentage points) with age.
    e. These patterns are comparable between males and females.
4. The 4-Digit Code uses a unique method for documenting GD across a patient's lifespan. Growth is ranked based on the section of the patient's growth curve, prenatal (birth) or postnatal (infancy-adulthood) that has the lowest height percentile. Using this approach on the 1162 patients with growth measures at birth and diagnosis:
    a. 72% of Growth Ranks were based on postnatal growth.
    b. The height percentile was lowest at birth in only 28% of subjects.

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5. Although GD is caused by many risk factors including prenatal tobacco exposure, the 4-Digit Code Growth Rank uniquely captures the GD associated with PAE because:
    a. Prenatal tobacco exposure impairs prenatal growth, not postnatal growth. This is reported in the literature [12] and observed in our dataset.
    b. PAE impairs postnatal growth, not prenatal growth, with its greatest impact on postnatal short stature. This is reported in the literature [9] and observed in our dataset.
    c. Since the 4-Digit Code ranks growth based on the age when the height percentile was lowest, this resulted in 82% of the growth ranks for 1814 subjects being derived from postnatal measures of growth. Since tobacco does not influence postnatal growth, this explains why the 4-Digit Growth Rank is significantly correlated with PAE and not with prenatal tobacco exposure in our dataset.
    d. Postnatal risks (neglect, abuse, multiple home placements) did not impair postnatal height percentiles, but were associated with a slight increase in weight percentiles.
6. GD is as highly correlated with severe CNS dysfunction as the FAS facial phenotype.
    a. The prevalence of severe CNS dysfunction (CNS Rank 3) increased significantly and linearly with increasing Growth Rank (Growth Rank 1 (32%); Rank 2 (39%); Rank 3 3 (49%); Rank 4 (60%)).
    b. The prevalence of severe CNS dysfunction (CNS Rank 3) increased significantly and linearly with increasing Face Rank(Face Rank 1, 30%; Rank 2, 34%; Rank 3, 44%; Rank 4, 68%).
7. Growth Rank is as predictive of severe CNS dysfunction as the 4-Digit Code FAS Face Rank.
    a. Individuals with Growth Ranks 3 and 4 (height and/or weight $\leqq$ third percentile) had a two to three-fold increased risk for severe CNS dysfunction. This finding was statistically significant.
    b. Individuals with Face Ranks 3 and 4 (2.5 to all 3 of the FAS facial features) had a two to five-fold increased risk for severe CNS dysfunction. This finding was statistically significant.
    c. GD was especially powerful in predicting which infants/toddlers with PAE and normal early development presented with severe CNS dysfunction later in childhood.
8. GD is highly correlated, but not highly concordant, with the FAS facial phenotype and microcephaly.
    a. Mean height and weight percentiles at birth, and at the age of diagnosis, decreased significantly with increasing severity of the FAS facial phenotype.
    b. The prevalence and magnitude of microcephaly increased significantly with increasing magnitude of GD.
    c. Despite these significant correlations, most patients with GD (83% and 71%, respectively) do not have the Rank 4 FAS facial phenotype or microcephaly. Thus, it is necessary to document GD to identify most individuals with PAE at risk for severe CNS dysfunction.

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Letter to the Editor Regarding Coles, Gailey, Mulle, Kable, Lynch, and Jones (2016): A Comparison Among 5 Methods for the Clinical Diagnosis of Fetal Alcohol Spectrum Disorders

Susan Astley

To the Editor:

IN THIS LETTER to the Editor, I discuss a study conducted by Coles and colleagues (2016) that took on the important task of comparing the outcomes of 5 fetal alcohol spectrum disorder (FASD) diagnostic systems when retroactively applied to the records of 1,581 patients. Valid comparisons require valid administration of each diagnostic system. The purpose of this Letter to the Editor is to share with readers the methods used, but not reported, that influenced the outcomes of this study. These additional details will allow readers to more accurately interpret this study.

Coles and colleagues (2016) applied 5 FASD diagnostic systems: Emory, FASD 4-Digit Code, CDC, Canadian, and Hoyme (Astley, 2004, 2013; Bertrand et al., 2004; Blackston et al., 2005; Chudley et al., 2005; Coles et al., 1997; Hoyme et al., 2005) to the records of 1,581 patients. These patients received an evaluation at the Emory clinic for alcohol- and drug-exposed children between 1995 and 2011. Fifty-two percent of the population had a confirmed prenatal alcohol exposure and 46% of the population was African American. Data from records collected at the patient's evaluation were used to retrospectively render FASD diagnoses in accordance with the criteria for each diagnostic system. The purpose of their study was to compare the prevalence of fetal alcohol syndrome (FAS), partial FAS (pFAS), and alcohol-related neurodevelopmental disorder (ARND) across the 5 different diagnostic systems. The authors reported the percent of alcohol-related diagnoses by diagnostic system as follows:

- 4-Digit Code: FAS 0.25%, pFAS 12.97%
- Canada: FAS 1.83%, pFAS 10.31%
- CDC: FAS 4.74%, pFAS N/A
- Hoyme: FAS 12.21%p, FAS 22.83%
- Emory-20: FAS 13.73%p, FAS 16.13%

To derive these outcomes, the authors reported they administered the 4-Digit Code "fully consistent with instruction for clinical coding for this system (Astley, 2004) (Coles et al., 2016, p. 1004)." They went on to report "these 4-digit codes were then translated into diagnostic categories as recommended by this system (Astley, 2004)" (Coles et al., 2016, p. 1004). "In all cases when norms were required (e.g., palpebral fissure length, PFL), we used those recommended by the diagnostic systems themselves (Coles et al., 2016, p. 1001)." The authors offered to provide more detailed information on request.

Two outcomes caught my attention: (i) the strikingly low prevalence of FAS (0.25%) and (ii) the comparatively high prevalence of pFAS (12.97%) reported for the 4-Digit Code. These outcomes were in stark contrast to the diagnostic outcomes we observe in the University of Washington Fetal Alcohol Syndrome Diagnostic and Prevention Network (Astley, 2013). In our population of 2,496 patients with prenatal alcohol exposure receiving a FASD diagnostic evaluation using the 4-Digit Code between 1993 and 2016, the prevalence of FAS is 3.5% and the prevalence of pFAS is 5.5%. Our population is 7.4% African American. Their population was 46% African American. But the prevalence of FAS and pFAS is comparable across all races in our clinic population. The prevalence of prenatal alcohol exposure in their population was 52%; ours is 100%. If you recomputed the prevalence of FAS and pFAS among just those with prenatal alcohol exposure (FAS 0.48% and pFAS 24.94%), the prevalence estimates are even more discrepant from what we observe in our clinical population. In an effort to understand why their 4-Digit Code prevalence estimates were so discrepant from ours, I conversed with the authors and they were kind enough to provide me the following additional information regarding how they administered the 4-Digit Code. Below is how they redefined which 4-Digit Code Diagnostic Categories A-V were used to define each diagnosis.

- FAS: Categories A, B
- pFAS: Categories C, E, G

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- ARND: Categories F, H
- Other Diagnosis: Categories D, I to V

It is important to note that the 4-Digit Code case-defines pFAS as Diagnostic Category C only (Astley, 2004). Category C includes 20 different 4-Digit Code combinations that meet the 4-Digit Code's growth, facial, central nervous system (CNS), and alcohol exposure criteria for pFAS. In contrast, Coles and colleagues (2016) redefined the 4-Digit Code's diagnosis of pFAS to include diagnostic Categories C, E, and G. Diagnostic Category E is Sentinel Physical Findings/Static Encephalopathy/Alcohol-Exposed. Diagnostic Category G is Sentinel Physical Findings/Neurobehavioral Disorder/Alcohol-Exposed. Thus, in contrast to their published methods, the authors did not *translate the 4-Digit Codes into diagnostic categories as recommended by the system* (Astley, 2004). They redefined the 4-Digit Code's pFAS diagnosis. This increased the number of 4-Digit Codes that case-defined pFAS from 20 to 60, resulting in a substantially elevated prevalence of pFAS. In addition, although the authors reported they used the physical features and neurobehavioral deficit (defined as per each system), the physical features and neurobehavioral deficit for pFAS (as defined per the 4-Digit Code) were not used. For example, individuals in Diagnostic Category G have moderate CNS dysfunction. But, pFAS (as defined per the 4-Digit Code) requires severe CNS dysfunction. pFAS also requires the FAS facial phenotype be a Rank 3 or Rank 4. But, none of the individuals in Diagnostic Category E met this criterion.

The authors also reported that "In all cases when norms were required (e.g. PFL), we used those recommended by the diagnostic systems themselves" (Coles et al., 2016, p. 1001). This was not true for the 4-Digit Code. The 4-Digit Code requires African American PFL charts be used on African Americans (e.g., Iosub et al., 1985), because African Americans have PFLs that are significantly larger (2 to 3 mm larger) than Caucasians. This is illustrated in a study by Astley (2011). The authors used the Stromland Scandinavian (Caucasian) PFL charts (Stromland et al., 1999) on the 788 African Americans in their study population. In accordance with the 4-Digit Code, an individual must present with PFLs 2 or more standard deviations (SD) below the mean to meet 1 of the 3 required facial features for FAS. As African Americans have significantly larger PFLs than Caucasians, it would be near impossible for an African American to have PFLs 2 SDs below the mean on the Stromland Caucasian PFL chart. Their PFLs would have to be 3 to 4 SDs below the mean on an African American PFL chart to register as 2 SDs below the mean on the Stromland Caucasian PFL chart. As 46% of the authors' study population was African American (n = 788), use of the Stromland Caucasian PFL chart would have a significant impact on the prevalence estimates of FAS and pFAS. The prevalence of FAS would be substantially under estimated and prevalence of pFAS would be substantially over estimated. Upon request, the authors revealed the following FAS and pFAS diagnostic prevalence estimates for the 788 African American subjects who made up 46% of their study population:

- 4-Digit Code as revised by Coles and colleagues (2016): FAS n = 0 (0.0%), pFAS n = 119 (16.0%)
- Canadian: FAS n = 16 (2.2%), pFAS n = 85 (11.4%)
- CDC: FAS n = 39 (5.2%), pFAS N/A
- Hoyme: FAS n = 100 (13.5%), pFAS n = 175 (23.6%)
- Emory: FAS n = 117 (15.7%), pFAS n = 141 (19.0%)

As anticipated, not a single African American received a diagnosis of FAS using the 4-Digit Code. Also as anticipated, the prevalence of pFAS was unusually high (16%). The 4-Digit Code criterion for pFAS allows the PFL to be relaxed to 1 SD below the mean. The 4-Digit Code criteria for FAS requires the PFL to be 2 or more SDs below the mean. Use of the wrong PFL chart on the African Americans prevented them from meeting the −2 SD PFL criterion for FAS, but allowed many to meet the −1 SD PFL criterion for pFAS.

When the 4-Digit Code is administered in accordance with the published instructions, as it has been for patients evaluated in the UW FASDPN clinic over the past 24 years, the prevalence of FAS and pFAS among Caucasian and African American individuals with prenatal alcohol exposure is as follows: Caucasian (4% FAS, 6% pFAS) and African American (6% FAS, 10% pFAS). The prevalence of pFAS is higher than FAS, but <2-fold higher. In stark contrast, the revisions imposed on the 4-Digit Code by Coles and colleagues (2016) resulted in a prevalence of pFAS that was 52-fold higher than FAS (12.97% vs. 0.25%, respectively). The prevalence of pFAS relative to FAS for the other diagnostic systems ranged from <2-fold higher to 5-fold higher.

The Journal published an Erratum (2016) to alert Readers that the authors used a PFL growth chart for the 4-Digit Code that was not consistent with their published methods: "In all cases when norms were required (e.g. PFL), we used those recommended by the diagnostic systems themselves."

In the Erratum (2016), the authors expressed concern about the applicability of the Iosub PFL chart for African Americans. The chart is based on a relatively small sample (n = 170) and binned into age ranges (<1 year, 1 to 2, 3 to 5, and 6 to 15 years of age). Despite these constraints, the Iosub PFL chart is a more accurate reflection of African American PFLs than the Stromland Scandinavian (Caucasian) PFL chart. The 4-Digit Code uses the Iosub PFL chart because, to date, it is the only chart available for African Americans that addresses the full age span and it reports PFLs that are commensurate with other published African American PFL charts for adults, as detailed below. It is confirmed in both the published literature and in our 24-year clinical experience (Astley, 2011) that the PFL for African Americans is significantly larger (by 1.5 to 2.4 mm) than the Caucasian PFL. Starting at birth, Fuchs and colleagues (1980) reported the PFL was 1.5 mm longer among African American term

neonates (20.0 mm, 2.0 SD) compared to Caucasian neonates (18.5 mm, 1.3 SD). Among adults, Barretto and Mathog (1999) reported the PFL was 2.6 mm longer among African Americans (32.0 mm, 2.3 SD) compared to Caucasians (29.4 mm, 2.3 SD). Farkas and colleagues (2005) reported the PFL was 1.6 mm longer among African American adults (32.6 mm, 2.0 SD) compared to Caucasians (31.0 mm, 1.3 SD). Stromland and colleagues (1999) report the PFL for 18-year-old Scandinavians is 29.1 mm (1.6 SD), commensurate with the Caucasian PFL reported by Barretto and Mathog (1999) and Farkas and colleagues (2005). Iosub and colleagues (1985) report the PFL for African Americans 6 to 15 years of age is 33.0 mm (3.0 SD), commensurate with the African American PFL reported by Barretto and Mathog (1999) and Farkas and colleagues (2005). The magnitude of difference between African American and Caucasian PFLs necessitates the use of PFL charts normed to their respective races. African American PFL normal growth charts exist (Barretto and Mathog, 1999; Farkas et al., 2005; Fuchs et al., 1980; Iosub et al., 1985), but as we reported back in 2011 (Astley, 2011), would benefit from an update.

In conclusion, the prevalence of FAS, pFAS, and ARND reported for the 4-Digit Code do not reflect the 4-Digit Code or any published FASD diagnostic system. The 4-Digit Code case-definition for pFAS was substantially revised and the administration of the 4-Digit Code was not *fully consistent with instruction for clinical coding for this system,* as reported by the authors. As a result, the prevalence estimates for FAS, pFAS, and ARND reported for the 4-Digit Code cannot be validly compared to one another and cannot be validly compared to the diagnostic prevalence estimates reported for the other diagnostic systems.

CONFLICT OF INTEREST

The author declares she has no conflict of interest.

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Comparison of the FASD 4-Digit Code and Hoyme et al. 2016 FASD diagnostic guidelines

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Abstract

Background: As clinicians strive to achieve consensus worldwide on how best to diagnose fetal alcohol spectrum disorders (FASD), the most recent FASD diagnostic systems exhibit convergence and divergence. Applying these systems to a single clinical population illustrates contrasts between them, but validation studies are ultimately required to identify the best system. Currently, only the 4-Digit Code has published comprehensive validation studies.

Methods: The 4-Digit Code and Hoyme 2016 FASD systems were applied to the records of 1,392 patients evaluated for FASD at the University of Washington to: 1) Compare the diagnostic criteria and tools used by each system, 2) Compare the prevalence and concordance of diagnostic outcomes and assess measures of validity.

Results: Only 38% of patients received concordant diagnoses. The Hoyme criteria rendered half as many diagnoses under the umbrella of FASD (n=558) as the 4-Digit Code (n=1,092) and diagnosed a much higher proportion (53%) as fetal alcohol syndrome/partial fetal alcohol syndrome (FAS/PFAS) than the 4-Digit Code (7%). Key Hoyme factors contributing to discordance included relaxation of facial criteria (40% had the Hoyme FAS face, including patients with confirmed absence of alcohol exposure); setting alcohol exposure thresholds prevented 1/3 with confirmed exposure from receiving FAS/FASD diagnoses; and setting minimum age limits for Alcohol-Related Neurodevelopmental Disorder prevented 79% of alcohol-exposed infants with neurodevelopmental impairment a FASD diagnosis. The Hoyme Lip/Philtrum Guides differ substantively from the 4-Digit Lip-Philtrum Guides and thus are not valid for use with the 4-Digit Code.

Conclusions: All FASD diagnostic systems need to publish comprehensive validation studies to identify which is the most accurate, reproducible, and medically valid**.**

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Introduction

As the field of fetal alcohol spectrum disorders (FASD) strives to achieve consensus worldwide on how best to diagnose FASD, the most recent versions of published guidelines (4-Digit Code, 2004 [1]) Canadian, 2015 [2], Hoyme et al., 2016 [3], and Australian, 2016 [4]) show both convergence and divergence. The new Canadian and Australian systems share many features in common, but diverge substantially from the 4-Digit Code and Hoyme et al. systems by dropping the growth deficiency criteria [5] and adopting a nomenclature (FASD with the face, and FASD without the face) that no longer reflects the spectrum of outcome. The 4-Digit Code [1] and Hoyme et al. [3] criteria continue to generate a spectrum of diagnoses under the umbrella of FASD (fetal alcohol syndrome (FAS), partial FAS (PFAS), Alcohol Related Neurodevelopmental Disorder (ARND), Static Encephalopathy/Alcohol Exposed (SE/AE), Neurobehavioral Disorder/Alcohol Exposed (ND/AE), and Alcohol Related Birth Defects (ARBD)) and maintain the 3 original core diagnostic criteria (growth deficiency, facial anomalies, and CNS abnormalities). The 4-Digit Code and Hoyme et al. systems differ in their diagnostic nomenclature, diagnostic tools, and the specific criteria used to generate each diagnosis. Comparing the diagnostic outcomes generated by the different systems when applied to a single clinical population serves to illustrate the major contrasts and similarities between the systems, but empirical validation studies are ultimately needed to identify the best system.

The objectives of this study were to: (1) compare the tools and criteria used by the 4-Digit Code and Hoyme et al. 2016 FASD diagnostic systems; and (2) administer each system to the records of 1,392 patients to compare the prevalence of FASD diagnoses produced by each system, assess diagnostic concordance between the two systems, and compare measures of validity applied to each system.

The outcomes of Objective 1 helped guide the study design (methods and study population) for Objective 2. Thus, the methods and results for Objective 1 are presented first, followed by the methods and results for Objective 2.

Objective 1. Comparison of the diagnostic tools and Criteria

Methods

Tools

Lip-philtrum guides: Both diagnostic systems provide 5-point, pictorial lip-philtrum guides for ranking the magnitude of philtrum smoothness and upper lip thinness. The 4-Digit Code provides two guides: Lip-Philtrum Guide 1 for Caucasians and all races with thinner upper lips like Caucasian, and Lip-Philtrum Guide 2 for African Americans and all races with thicker upper lips like African Americans (Figures 1 and 2). Hoyme et al. have also introduced two lip/philtrum guides: the North American Lip/Philtrum Guide [3] produced from a U.S. white population and the South African Mixed Race Lip/Philtrum Guide [6] produced from a Cape Coloured (mixed race) population in the Western Cape Province (Figures 1 and 2).

Philtrum: The Rank 1-5 philtrums depicted on the 4-Digit Code Caucasian and Hoyme et al. North American guides were visually compared to determine if the magnitude of philtrum depth or smoothness depicted by each Rank was comparable between the two guides (e.g. was the Rank 4 philtrum smoothness depicted on the 4-Digit Guide the same as the Rank 4 philtrum smoothness depicted on the Hoyme et al. Guide?). This visual comparison was repeated for the 4-Digit African American and Hoyme et al. South African guides.

Upper lip: The Rank 1-5 lips depicted on the 4-Digit Code Caucasian and Hoyme et al. North American guides were compared using the objective, quantitative measure of lip thinness called lip circularity (perimeter2/area) generated by the FAS Facial Photographic Analysis Software [7]. Circularity is computed by outlining the vermilion border of the upper lip with the mouse (Figure 2C); the thinner the lip, the bigger the circularity.

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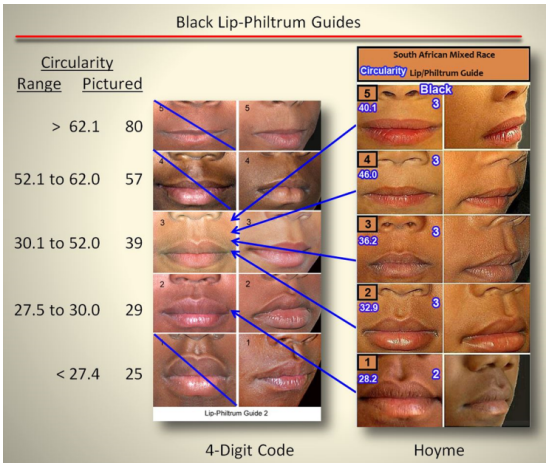

Figure 1. The Hoyme South-African Mixed-Race Lip/Philtrum Guide differs from the "African-American" 4-Digit Code Lip-Philtrum Guide 2

Upper lip: The objective measure of upper lip thinness (circularity = perimeter^2/area) is printed to the left of the 4-Digit Code Guide and in white font with a blue border on the Hoyme Guide. For example, the 4-Digit Code Rank 4 lip has a circularity of 57 and is defined by the range of circularities 52.1 to 62.0. The Hoyme Rank 4 lip has a circularity of 46.0, thus is equivalent to the 4-Digit Code Rank 3 lip. Circularity confirmed the Hoyme et al. Ranks 1, 2, 3, 4 and 5 lips were equivalent to the 4-Digit Ranks 2, 3, 3, 3, and 3 respectively. There are no lip images on the Hoyme et al. Guide that correspond to (fall within the circularity ranges that define) the 4-Digit Ranks 1, 4, or 5. Lips on the Hoyme et al. Guide do not increase in thinness in linear fashion as they do on the 4-Digit Code Guide 2. The Hoyme et al. Rank 5 lip is thicker (circularity 40.1) than the Hoyme et al. Rank 4 lip (circularity 46.0). Most importantly, the Hoyme et al. Rank 4 lip (the clinical cut-off for FAS) is thicker than the 4-Digit Code Rank 4 lip. The Hoyme et al. Rank 4 lip (circularity 46.0) falls within the circularity range depicted by the 4-Digit Rank 3 lip (30.1 to 52.0). The Hoyme et al. Rank 5 lip (circularity 40.1) is substantially thicker than the 4-Digit Rank 5 lip (circularity 80).
Philtrum: The Rank 1 through 5 philtrums depicted on both guides appeared broadly equivalent by visual inspection. Based on our findings and the findings of Hoyme et al. [6], the South African Mixed Race Lip/Philtrum Guide is not appropriate for use on an African American population. (South African Mixed Race Lip/Philtrum Guide used with permission from Wiley & Sons, Inc).

Lip Ranks 1-5 on the 4-Digit Code Lip-Philtrum Guides are case-defined by the range of lip circularities posted on the backside of each Lip-Philtrum Guide (Figure 2B). Lip circularity was computed for each lip on the Hoyme et al. North American Lip/Philtrum Guide. The lip circularities on the 4-Digit Code Caucasian and Hoyme et al. North American guides were compared to determine if the magnitude of lip thinness depicted by each Rank was comparable (e.g., was the Rank 4 lip thinness depicted on the 4-Digit Caucasian Guide the same as the Rank 4 lip thinness depicted on the Hoyme et al. North American Guide?). This comparison of lip circularities was repeated for the 4-Digit Code African American and Hoyme et al. South African guides

Facial analysis software: The 4-Digit Code advises measuring the facial features from 2D digital photos using the FAS Facial Photographic Analysis Software [7]. The authors of the Hoyme et al. system "feel direct examinations of facial features are more practical in an office setting." Since empirical studies have already confirmed the superior accuracy of the photo versus direct method of facial measurement [8, 9], a formal assessment of photo versus direct measurement of facial features was not repeated in this study.

Diagnostic nomenclature and criteria

Figures were created to illustrate the key contrasts between the diagnoses generated by each system, the nomenclature assigned to each diagnosis, and the diagnostic criteria.

Results

Tools: Contrasts in lip-philtrum guides

The Hoyme et al 2015 South African Mixed Race Lip/Philtrum Guide [6] does not match the "African American" 4-Digit Code Lip-Philtrum Guide 2 (Figure 1).

Philtrum: The Rank 1 through 5 philtrums depicted on both guides appeared broadly equivalent by visual inspection.

Upper lip: Circularity confirms the Hoyme et al. Rank 4 lip (the clinical cut-off for FAS) is thicker than the 4-Digit Code Rank 4 lip (e.g., it is equivalent to the 4-Digit Code Rank 3 lip).

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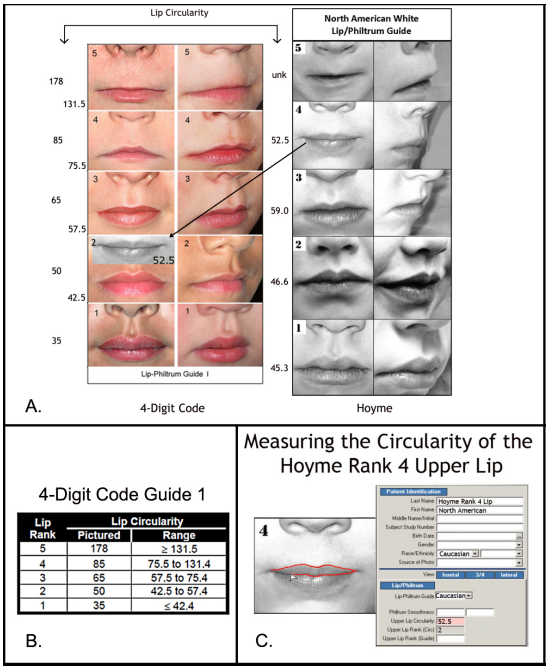

Figure 2. The Hoyme North-American White Lip/Philtrum Guide differs from the 4-Digit Code "Caucasian" Lip-Philtrum Guide 1

The Rank 1 through 5 philtrums depicted on both Guides appear broadly equivalent, but the upper lips are substantially different. A) Lip circularity (perimeter^2/area) is printed to the left of each guide. B) The range of circularities that define each 4-Digit Code Lip Rank are presented in the Lip Circularity table printed on the backside of the 4-Digit Code Lip-Philtrum Guide. C) The FAS Facial Photographic Analysis Software [7] computes circularity when the User outlines the vermilion border of the upper lip (click on video link for demonstration https://youtu.be/6SbiXF220PM). Lip circularity confirms that the Hoyme et al. Rank 1, 2, 3, 4 and 5 upper lips are equivalent to the 4-Digit Code Ranks 2, 2, 3, 2 and 5 respectively. There is no lip image on the Hoyme et al. Guide that reflects the 4-Digit Rank 1 or Rank 4 lips. The lips on the 4-Digit Guide become progressively thinner (circularity becomes progressively larger) with increasing Rank. This is not true for the Hoyme et al. Guide. The circularity of the Hoyme et al. Rank 4 lip (the clinical cut-off for FAS) is 52.5, confirming it falls within the circularity range of the 4-Digit Code Rank 2 lip. The black and white overlay (A) of the Hoyme et al. Rank 4 lip on the 4-Digit Code Guide 1 demonstrates both visually and numerically that the Hoyme et al. Rank 4 lip is substantially thicker than the 4-Digit Code Rank 4 lip. This analysis confirms the Hoyme et al. North American White Lip/Philtrum Guide is not a valid tool for use with the FASD 4-Digit Diagnostic Code.(North American White Lip/Philtrum Guide used with permission from the American Academy of Pediatrics).

Unlike the 4-Digit Code Lip-Philtrum Guide, the lips pictured on the Hoyme et al. Guide do not progressively become thinner as Rank increases and no lip on the Hoyme et al. Guide is equivalent to the 4-Digit Code Rank 1, 4 or 5 lips. Based on our findings here and the findings of Hoyme et al. [6], the South African Mixed Race Lip/Philtrum Guide is not appropriate for use on an African American population and thus was not used to address Study Objective 2. The study population for Objective 2 was adjusted accordingly (as described below) to accommodate this finding.

The Hoyme et al. 2016 [3] North American White Lip/Philtrum Guide does not match the "Caucasian" 4-Digit Code Lip-Philtrum Guide 1 (Figure 2).

Philtrum: The Rank 1 through 5 philtrums depicted on both guides appeared broadly equivalent by visual inspection.

Upper lip: Circularity (perimeter^2/area) confirms the Hoyme et al. Rank 4 lip (the clinical cut-off for FAS) is substantially thicker than the 4-Digit Code Rank 4 lip (e.g., it is equivalent to the 4-Digit Code Rank 2 lip). The 4-Digit Code defines the Rank 2 lip as within the normal range, slightly thicker than the population mean depicted by Lip Rank 3. Unlike the 4-Digit Code Lip-Philtrum Guide 1, the lips pictured on the Hoyme et al. Guide do not progressively become thinner as Rank increases and no lip on the Hoyme et al. Guide is equivalent to the 4-Digit Code Rank 1 or Rank 4 lips.

Despite the contrasts between the two lip/philtrum guides, both are intended for use on North American Caucasian populations and thus were used to address Objective 2 below.

Contrasts in diagnoses and nomenclature

The key contrasts between the 4-Digit Code and Hoyme et al diagnoses and nomenclature are highlighted in Figures 3 and 4, respectively.

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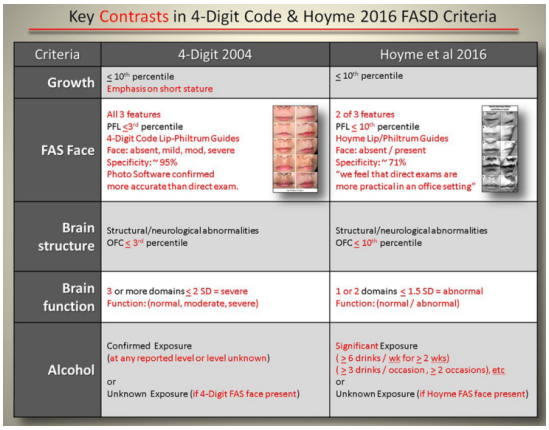

Figure 3. Key contrasts between the 4-Digit Code and Hoyme et al. 2016 FASD diagnostic criteria

Key contrasts between the two diagnostic systems are presented in red font. Full criteria are presented in the 4-Digit Code [1] and Hoyme et al. [3] published guidelines.

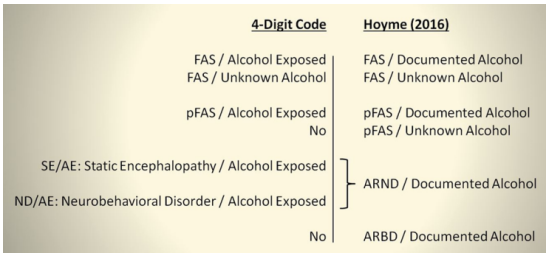

Figure 4. Key contrasts between the 4-Digit Code and Hoyme FASD diagnostic nomenclature

The 4-Digit Code [1] defines five FASD diagnostic categories, the Hoyme et al. [3} defines six. Although both diagnostic systems have three diagnostic categories that share the same name, the criteria used to define each are markedly different between the two systems. The 4-Digit Code does not include diagnostic categories labeled pFAS/Unknown Alcohol or ARBD. The diagnosis SE/AE is defined by severe structural and/or functional CNS abnormalities, but lacks the physical characteristics that would qualify for FAS or pFAS. ND/AE is defined by moderate functional CNS abnormalities. The CNS functional abnormalities of ARND are broadly equivalent to the moderate and severe CNS functional abnormalities defined by ND/AE and SE/AE combined. The 4-Digit Code Diagnostic Categories that case-define each diagnosis [1] are as follows: FAS/Alcohol Exposed (Category A); FAS/Unknown Alcohol (B); PFAS/Alcohol Exposed (C); SE/AE (E,F); and ND/AE (G,H).

ARND: Alcohol Related Neurodevelopmental Disorder; ARBD: Alcohol Related Birth Defects; FAS: fetal alcohol syndrome; FASD: fetal alcohol spectrum disorders; ND/AE: neurobehavioral disorder/alcohol exposed; pFAS: partial fetal alcohol syndrome; SE/AE: static encephalopathy/alcohol exposed.

Contrasts in diagnostic criteria

Growth deficiency: The Hoyme et al criteria use the same cut-off (prenatal or postnatal height and/or weight ≤ 10th percentile) to define growth deficiency as the 4-Digit Code, but the Hoyme et al. criteria classify growth deficiency on a dichotomous scale (present/absent), whereas the 4-Digit Code ranks growth deficiency on a 4-point ordinal scale with emphasis on short stature; a method that is confirmed to be highly predictive of CNS dysfunction [5].

Facial phenotype: When compared to the 4-Digit Code Rank 4 FAS facial phenotype, the Hoyme et al. FAS facial phenotype is substantially relaxed. This is best illustrated using the 4-Digit Code Facial ABC-Score printed on the backside of the 4-Digit Code "Caucasian" Lip-Philtrum Guide 1 (Figure 5). The 4-Digit Code FAS facial phenotype is defined by a single ABC-Score (Facial ABC-Score CCC, Face Rank 4) (Figure 5A). The three letters "CCC" reflect the magnitude of expression of the short palpebral fissure length (PFL), smooth philtrum, and thin upper lip in that order. C reflects severe expression in the FAS range, B reflects moderate expression, and A reflects normal expression. The Hoyme et al. FAS facial criteria are relaxed relative to the 4-Digit Code in three ways:

1. Only 2 of 3 cardinal features are required.

2. The PFL is relaxed to the 10th percentile.

3. As shown in our analysis above, the Rank 4 lip on the Hoyme et al. North American Lip/Philtrum Guide has a circularity equivalent to the Rank 2 lip on the 4-Digit Lip-Philtrum Guide 1.

This results in almost every 4-Digit Code Facial ABC-Score meeting the relaxed Hoyme et al. facial criteria (Figure 5B) including 13 of the 15 ABC-Scores that depict the 4-Digit Code Rank 2 (mild) facial phenotype and 3 of the 8 ABC-Scores that depict the complete absence of all three FAS facial features (Rank 1). Clinically, the 4-Digit Code classifies Rank 1 and 2 facial phenotypes as being within the normal range. The practical clinical impact of this relaxation is illustrated in Figure 6 in which an adolescent with high function (e.g., FSIQ 123) and confirmed absence of prenatal alcohol

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exposure met the Hoyme et al. criteria for the full FAS facial phenotype.

In addition to the contrasts in facial criteria, the scales of measurement used to clinically classify the facial phenotype also differ. The 4-Digit Code documents the full continuum of expression of the FAS facial phenotype (Face Ranks 1 through 4), a continuum confirmed to be highly predictive of CNS dysfunction [5, 10]. In contrast, the Hoyme et al system documents the facial phenotype as simply present or absent.

CNS dysfunction: The Hoyme et al. criteria that define neurobehavioral impairment (broadly defined as at least one neurobehavioral domain >1.5 standard deviations (SD) below the mean) appeared broadly equivalent to the 4-Digit Code criteria for moderate to severe CNS dysfunction (CNS Ranks 2 and 3). CNS Rank 3 (severe dysfunction, labeled Static Encephalopathy) is defined by 3 or more domains of function, 2 or more SDs below the mean. CNS Rank 2 (moderate dysfunction, labeled Neurobehavioral Disorder) is defined by at least one domain of function between 1 and 2 SDs below the mean, and not more than 3 domains of function 2 or more SDs below the mean. CNS Rank 1 reflects normal function across all domains [1]. Validation studies confirm CNS Ranks 1, 2 and 3 are significantly and linearly correlated with the severity of underlying CNS structural abnormalities, the magnitude of expression of the FAS facial phenotype, and the level of prenatal alcohol exposure [11].

CNS structural abnormalities: The Hoyme et al. criteria for deficient brain growth, abnormal morphogenesis, or abnormal neurophysiology were largely equivalent to the 4-Digit Code criteria for CNS structural and neurological abnormalities (CNS Rank 4) with the exception of the cut-off used to define microcephaly (Hoyme et al. criteria: ≤ 10th percentile; 4-Digit Code: ≤ 3rd percentile).

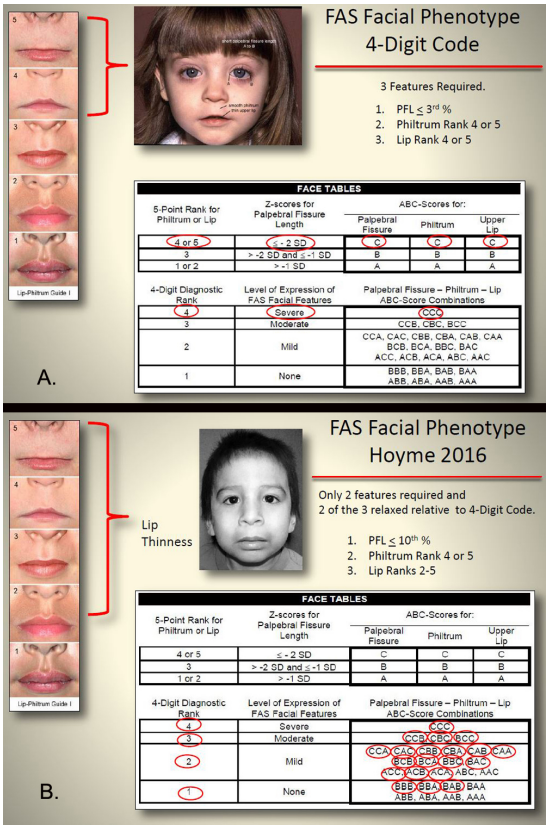

Figure 5. The Hoyme FAS face is substantially relaxed relative to the 4-Digit Code FAS face.

A) The 4-Digit Code uses the Facial ABC-Score to document all combinations of expression of the 3 FAS facial features. These ABC-Scores are clustered to define the 4-Digit Code Face Ranks 1-4. The 4-Digit Code FAS facial phenotype is defined by a single ABC-Score (Facial ABC-Score CCC, Face Rank 4). **B)** In contrast, the relaxation of the Hoyme et al. FAS facial criteria (e.g., only 2 of 3 features required, PFL relaxed to 10th percentile, and Rank 4 lip relaxed to 4-Digit Rank 2 lip) results in most every 4-Digit Code Facial ABC-Score meeting the relaxed criteria, including ABC-Scores that define Face Ranks 1 and 2. Clinically, the 4-Digit Code classifies Rank 1 and 2 facial phenotypes as being within the normal range. (FAS facial phenotype from Hoyme et al, 2016 used with permission from the American Academy of Pediatrics).

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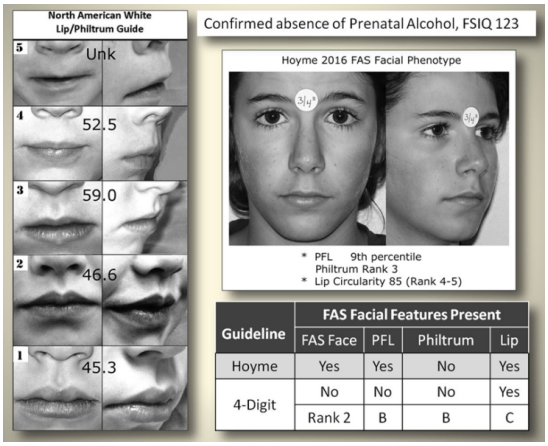

Figure 6. The Hoyme FAS facial criteria are so relaxed even individuals with confirmed absence of prenatal alcohol exposure meet the criteria.

When the Hoyme et al. [3] FAS facial criteria were applied to an adolescent with high function (FSIQ 123) and confirmed absence of prenatal alcohol exposure, the adolescent met the Hoyme et al. criteria for the full FAS facial phenotype. When measured directly and with the FAS Facial Photographic Analysis Software, she presented with 2 of the 3 features: palpebral fissure length (PFL) ≤10th percentile using the Stromland Caucasian PFL charts and a thin upper lip ≥ Rank 4 on the Hoyme North American Lip/Philtrum Guide. Both visual inspection and lip circularity (85) confirm her lip was as thin or thinner than the Hoyme Rank 4 lip (circularity 52.5). In contrast, the 4-Digit Code FAS facial criteria classified her within the normal range (Face ABC-Score BBC, Face Rank 2), presenting with just 1 of the 3 features in the FAS range (a thin upper lip, 4-Digit Code Lip Rank 4).

Alcohol exposure: The Hoyme et al., criteria for documented prenatal alcohol exposure are more stringent overall than the 4-Digit Code and include thresholds (≥6 drinks/week for ≥2 weeks during pregnancy or ≥3 drinks per occasion on ≥2 occasions during pregnancy). The 4-Digit Code requires a confirmed exposure, but does not set thresholds because recall and reporting of quantity, frequency, and timing of exposure have been confirmed highly unreliable in a clinical setting and exposure below a designated threshold has not been confirmed safe for all fetuses [11]. The Hoyme et al. system allows FAS and PFAS to be diagnosed when exposure is unknown. The 4-Digit Code allows FAS to be diagnosed when exposure is unknown because FAS requires the presence of the Rank 4 FAS facial phenotype and the Rank 4 face is confirmed to be highly specific to (caused only by) prenatal alcohol exposure [11].

Objective 2: Comparison of diagnostic outcomes

Methods

Study population

The records of 1,392 patients were drawn from 1,522 consecutive patients that received an FASD diagnostic evaluation at the University of Washington Fetal Alcohol Syndrome Diagnostic & Prevention Network (FASDPN). The diagnostic evaluations were performed by an interdisciplinary team between 1993 and 2012 using the FASD 4-Digit Code [1]. The interdisciplinary team included a medical doctor, psychologist, occupational therapist, speech language pathologist, social worker, family advocate, and public health professional [11, 12]. All patients with one or both birth parents African American (130 of the 1,522) were excluded from the study because it was unclear which PFL normal growth chart to use for African Americans when applying the Hoyme et al. system [13] and our findings in Objective 1 and those reported by Hoyme et al. [6] confirm the South African Mixed Race Lip/Philtrum Guide is inappropriate for use on an African American population.

Historically, all records resulting from each patient's FASD diagnostic evaluation have been entered into a research database since 1992 with University of Washington Human Subjects approval and patient consent. Over 95% of patients provide consent for their clinical data to be used for research purposes. Patients' records include the following standardized 4-Digit Code data forms: the New Patient Information Form, the FASD Diagnostic Form, digital facial photos, and the FAS Facial Photographic Analysis Report [1, 7]. These data are entered into a research database shortly after the patient's FASD diagnostic evaluation reflecting the tools and growth norms available at that time. Over the decades the 4-Digit Code has evolved (First edition 1997, Third edition 2004) [1, 14-16], new

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tools have been developed like the FAS Facial Photographic Analysis Software (Version 1.0 in 2004, Version 2.1 in 2016) [7], and new more accurate growth norms have been adopted (CDC growth charts [17] and Stromland Scandinavian PFL charts [18].

For the purposes of research, all patients' clinical 4-Digit Codes are updated to "research" 4-Digit Codes to reflect the most current tools and norms available at the time of the research study. For this study, all 4-Digit Codes were updated to reflect the most current third edition of the 4-Digit Code [1].

Application of the diagnostic tools and norms

The following tools and norms were used to update the 4-Digit Code FASD diagnoses and generate the Hoyme et al. [3] FASD diagnoses. The Reader is encouraged to familiarize themselves with the diagnostic criteria specific to each diagnostic system [1, 3] as space does not permit replication of the criteria here.

Growth: The Hoyme et al. criteria use the same cut-off (prenatal or postnatal height and/or weight ≤ 10th percentile) to define growth deficiency as the 4-Digit Code, thus all patients with 4-Digit Code Growth Ranks 2,3 or 4 were classified as meeting the Hoyme et al. growth deficiency criteria.

Height and weight normal growth charts: Height and weight percentiles were generated from the Hall [19] birth weight and length growth charts by gestational age; the World Health Organization (WHO) [20] height and weight growth charts for children 0–2 years of age, and the Centers for Disease Control (CDC) 2000 [17] height and weight growth charts for patients 2 years of age and older. The height percentile was adjusted for mid-parental height [21] when both parents' heights were reported.

Facial features: At the time of each patient's FASD diagnostic evaluation, three standardized, digital facial photographs (Figure 7) were taken and measured using the FAS Facial Photographic Analysis Software [7]. As a result, each patient's research record included the following facial measures: PFLs in millimeters, philtrum smoothness (Rank 1 to 5 on the 4-Digit Code Lip-Philtrum Guide 1) and upper lip circularity (perimeter^2/area) and corresponding Lip Rank (Rank 1 to 5 on the 4-Digit Code Lip-Philtrum Guide 1).

PFL: For the purposes of this research study, all PFL z-scores were updated to reflect the Stromland Scandinavian PFL growth charts. The Stromland charts are confirmed valid for use on a North American population [8] and address the full age span (birth through adult) represented in our study population. In addition, the Stromland PFL growth charts were generated from digital images, thus meeting the recommendation by Hoyme et al. [3] that PFLs measured from photos should be compared to PFL normal growth charts generated from photos.

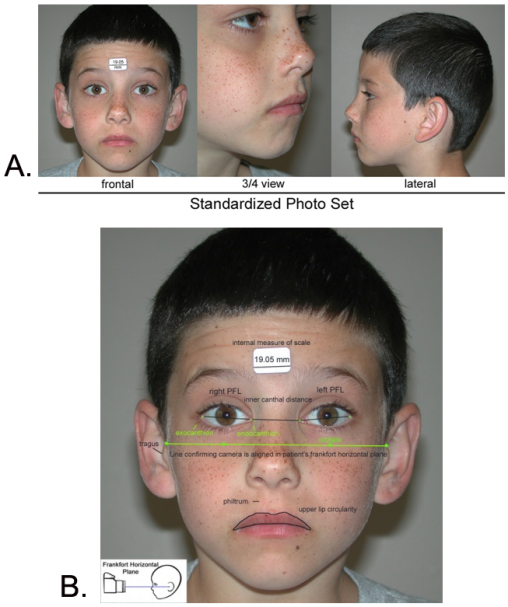

Figure 7. The FAS Facial Photographic Analysis Software was used to measure the 3 FAS facial features.

A) The palpebral fissure length (PFL), philtrum smoothness, and upper lip thinness are measured from three standardized, digital photographs. B) Standardization includes proper rotation, exposure, focus, and facial expression. An internal measure of scale (a 3/4 inch (19.05 mm) paper sticker) is placed on the forehead to measure the PFLs in millimeters.

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Philtrum smoothness and upper lip thinness: The 4-Digit Code "Caucasian" Lip-Philtrum Guide 1 and the Hoyme et al. North American Lip/Philtrum Guide were used to rank philtrum smoothness and lip thinness. Since the images depicting the Rank 1 through 5 philtrums on the 4-Digit Code and Hoyme et al. guides appeared broadly equivalent (per Objective 1), the philtrum rank assigned at the time of diagnosis using the 4-Digit Code guide was the same philtrum rank assigned to the patient using the Hoyme et al. guide (Figure 2) (e.g., if the patient had a Rank 4 philtrum using the 4-Digit Code guide, they received a Rank 4 philtrum using the Hoyme et al. guide). In contrast, the analyses in Objective 1 confirmed the Rank 1 through 5 images depicting upper lip thinness did not match between the 4-Digit Guide 1 and the Hoyme et al. North American Guide (Figure 2). The 4-Digit Code uses the full range of Lip Ranks 1-5 to classify the FAS facial phenotype on a 4-point Likert scale from normal (Face Rank 1) to severe FAS (Face Rank 4). In contrast, the Hoyme et al. FAS/PFAS facial criteria measure lip thinness on a dichotomous scale (thin: ≥Rank 4, not thin: <Rank 4) to classify the FAS/PFAS facial phenotype on a dichotomous scale (present, absent). To accurately and objectively identify which patients met the Hoyme et al. diagnostic criteria for a thin upper lip (≥Rank 4), the Rank 4 upper lip on the Hoyme et al. North American Lip/Philtrum Guide was outlined using the facial software. The video clip in Figure 2C demonstrates this procedure. The circularity of the Hoyme et al. Rank 4 lip was 52.5; equivalent to the 4-Digit Rank 2 lip (defined by the circularity range 42.5 to 57.4). Thus all patients with an upper lip circularity of 52.5 or greater met the Hoyme et al. criteria for a thin upper lip (Rank 4 or 5 on the Hoyme et al. North American Lip/Philtrum Guide).

CNS dysfunction: Based on our findings in Objective 1, all patients with 4-Digit Code CNS Ranks of 2 or 3 (moderate to severe CNS dysfunction) were classified as meeting the Hoyme et al. criteria for neurobehavioral impairment.

CNS structural abnormalities: Based on our findings in Objective 1, all patients with a 4-Digit Code CNS Rank 4 (structural/neurological abnormalities) were classified as meeting the Hoyme et al. criteria for deficient brain growth, abnormal morphogenesis, or abnormal neurophysiology. In addition, all patients with an occipital frontal circumference (OFC) ≤10th percentile were classified as meeting the Hoyme et al. CNS criteria. The WHO [20] OFC charts for children 0-5 years of age and the Nellhaus [22] OFC growth charts for children 5-18 years of age were used.

Alcohol related birth defects (ARBD): The Hoyme et al. diagnosis labeled ARBD is not recognized in the 4-Digit Code or any FASD diagnostic system introduced subsequent to the 1996 Institute of Medicine FASD diagnostic guidelines [12, 23]. For this reason, this diagnostic classification was not included in this study.

Statistical analyses

Descriptive statistics (valid percentages) were used to profile the study population. Chi-square tests were used to compare groups and linear trends across groups for outcomes measured on nominal or ordinal scales. One-way analysis of variance (ANOVA) was used to compare means and detect linear trends across three or more groups when outcomes were measured on a continuous scale. T-tests were used to compare means between two independent groups.

Results

Objective 2: Compare the diagnostic outcomes between the two systems.

Study population

The socio-demographic profile of the study population (n=1,392) is presented in Table 1. The population spanned the entire age range from newborn to adult with 57% Caucasian and 44% female.

Objective 2a: Compare the prevalence of FASD diagnostic outcomes generated by each system

The 4-Digit Code classified 78% (1,092/1,392) of the patients broadly under the umbrella of FASD (FAS, PFAS, SE/AE, and ND/AE) (Figure 8A). The prevalence of FAS and PFAS was 2% (n=28) and

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4% (n=53), respectively. In contrast, the Hoyme et al. system classified only 40% (558/1,392) of the patients under the umbrella of FASD. The prevalence of FAS (6%; n=89) and PFAS (15%, n=208) generated by the Hoyme et al. system was 3- to 4-fold greater than the prevalence of FAS and PFAS generated by the 4-Digit Code.

Table 1. Sociodemographic and exposure profile of the study population (n = 1,392)

Characteristic	N	Valid %
Gender		
Female	608	44%
Male	784	56%
Race/ethnicity		
Caucasian	788	57%
Native American	126	9%
Hispanic	37	3%
African American	0	0%
Other	434	31%
Age at FASD diagnostic evaluation (years)		
0-2	141	10%
3-5	314	23%
6-7	234	17%
8-12	411	30%
13-18	236	17%
19+	56	4%
Prenatal Alcohol Exposure		
Confirmed (4-Digit Code Ranks 3 and 4)	1,117	85%
Unknown (4-Digit Code Rank 2)	215	15%

Thirty-five percent (379/1,092) of the patients who received a diagnosis of FASD using the 4-Digit Code did not receive a diagnosis of FASD using the Hoyme et al. system (Figure 8B). They all had confirmed prenatal alcohol exposures (e.g., birth mother reported drinking throughout the pregnancy), but their record of exposure did not meet the more stringent criteria (e.g., intoxication confirmed by BAC; positive biomarker test like analysis of FAEE; positive outcome on a validated screening tool like the T-ACE or AUDIT; or number of drinks per week or occasion reported) or the level of exposure (e.g., ≥ 6 drinks/week or ≥ 2 weeks or ≥2 drinks/occasion on ≥ 2 occasions) required by the Hoyme et al. system. In some cases, as illustrated in Figure 9, a patient diagnosed with severe FAS (4-Digit Code 4443) did not receive a diagnosis under the umbrella of FASD using the Hoyme et al. system because the exposure level reported directly by the birth mother (1 drink/week throughout pregnancy) was not high enough to meet the Hoyme et al. alcohol-exposure criteria (≥6 drinks/week for ≥2 weeks during pregnancy).

Among the subset of 141 alcohol-exposed patients under 3 years of age, the 4-Digit Code classified 70% (98/141) under the umbrella of FASD (Figure 8C). The prevalence of SE/AE and ND/AE was 21% (n=29) and 41% (n=58) respectively. In contrast, the Hoyme et al. system classified only 15% (21/141) under the umbrella of FASD. No infant/toddler received a diagnosis of ARND because the Hoyme et al. system does not permit a diagnosis of ARND in patients less than 3 years of age.

Objective 2b: Assess diagnostic concordance between the two systems

Diagnostic concordance was observed in 38% (n=528) of the 1,392 patients (Figure 10). The two diagnostic systems ruled-out FASD in 239 patients and both rendered the same diagnosis under the umbrella of FASD for 289 patients. Diagnostic discordance was observed in 62% (n=864) of the 1,392 patients. The discordance ranged from subtle differences (e.g., the patient received a diagnosis of FAS by one system and PFAS by the other system) to marked contrasts (e.g., the patient received a diagnosis of FAS by one system and no diagnosis under the umbrella of FASD by the other system).

To illustrate some of the more striking contrasts, of the 21 patients that received a diagnosis of FAS/Alcohol Exposed using the 4-Digit Code, 10 had FASD ruled-out altogether using the Hoyme et al. system (see the 4-Digit Code FAS/AE column in Figure 10). All 10 patients were less than 5 years of age. They presented with CNS structural abnormalities (e.g., microcephaly: OFC ≤ 3rd percentile), but early development was broadly within the normal range. All ten were too young to engage in the necessary level of testing to accurately rule-out moderate or severe CNS dysfunction. The Hoyme et al. system require both CNS structural abnormalities (e.g., OFC ≤ 10th percentile) and evidence of CNS dysfunction for a diagnosis of FAS.

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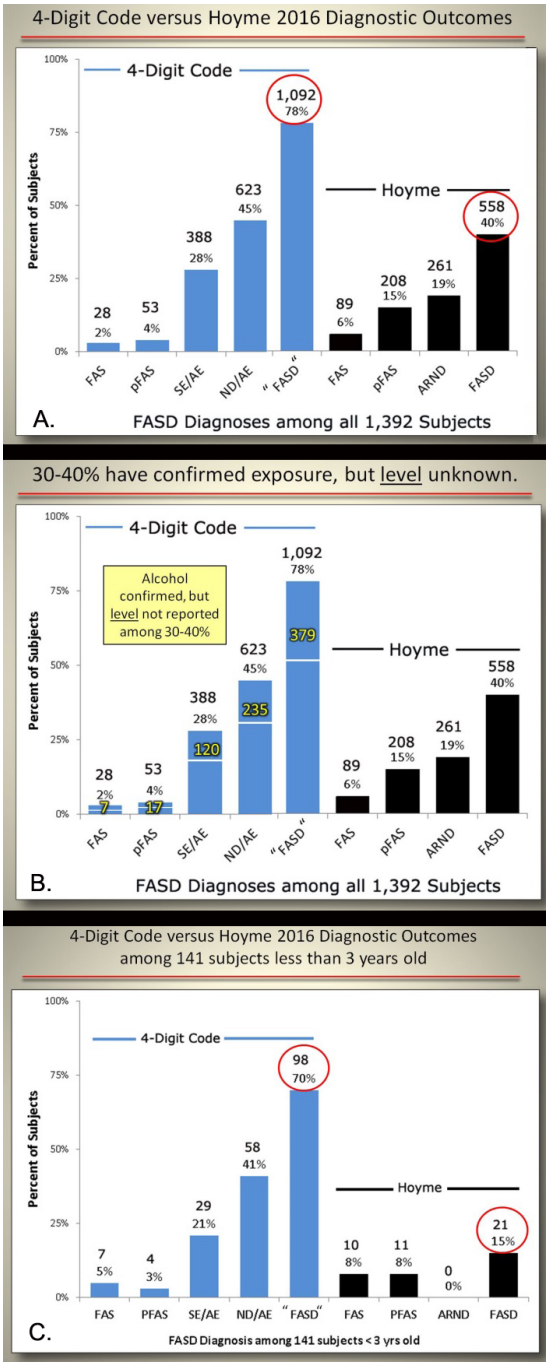

Figure 8. Contrasts in diagnostic outcomes when the 4-Digit Code and Hoyme FASD diagnostic systems were applied.

A) Contrast in outcomes among all 1,392 patients. B) The impact of the more stringent Hoyme et al. [3] alcohol exposure criteria on the outcomes. The numbers in yellow document the number of patients with confirmed prenatal alcohol exposure that did not meet the more stringent Hoyme et al. criteria. For example, if the more stringent Hoyme et al. alcohol criteria were applied, 379 of the 1,092 would not have received a FASD diagnosis using the 4-Digit Code. C) Contrast in outcomes among the subset of 141 patients who were less than 3 years of age at the time of diagnosis. No infant/toddler received a diagnosis of ARND because the Hoyme et al. system does not permit a diagnosis of ARND in patients less than 3 years of age.
FAS: fetal alcohol syndrome; pFAS: partial fetal alcohol syndrome; SE/AE: static encephalopathy/alcohol exposed; ND/AE: neurobehavioral disorder/alcohol exposed; FASD: fetal alcohol spectrum disorders; ARND: alcohol related birth defects.

An Actual Case of Full FAS (4443) in a 21 year old		
Growth	Rank 4	Height 1%, Weight 1%
Face	FAS Rank 4 (CCC)	PFL 1%, Philtrum Rank 4, Lip Rank 4
CNS structure	CNS Rank 4	Microcephaly 2 %
CNS dysfunction	CNS Rank 3, Severe	FSIQ 76, Adaptation 65, Math Calc 60, Core Lang 67, Memory 59
Alcohol	Rank 3 Birth mother report	1 drink/wk for > 2 wk during pregnancy (all 3 trimesters) 1 drink per occasion on > 2 occasions during pregnancy

Figure 9. FAS does occur when the reported alcohol exposure is below the Hoyme et al. threshold.

The outcomes displayed reflect an actual case of full FAS with confirmed prenatal alcohol exposure (4-Digit Code 4443) in a 21-year-old diagnosed at the University of Washington. This example demonstrates that FAS does occur when *reported* alcohol is less than the threshold (≥6 drinks/week for ≥2 weeks during pregnancy and/or ≥3 drinks per occasion on ≥2 occasions during pregnancy) required by the Hoyme et al. [3] FASD diagnostic system. The outcomes reported for CNS dysfunction are standard scores (mean 100, SD 15) for measures of cognition, adaptation, math calculation, core language skills, and memory.
CNS: central nervous system; PFL: palpebral fissure length.

Among the 208 patients that were classified "Not FASD" by the 4-Digit Code, 39 received a FAS (n=16) or PFAS (n=23) diagnosis using the Hoyme et al. system (Figure 10). The 4-Digit Code does not render a diagnosis under the umbrella of FASD if: 1) alcohol exposure is unknown and 2) the Rank 4 FAS face is absent. If an individual does not have a confirmed prenatal alcohol exposure, the 4-Digit Code Rank 4 FAS face can serve as confirmation of exposure because the phenotype is confirmed to be so highly specific to (caused only by) prenatal

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alcohol exposure (>95% specificity) [11]. The Hoyme et al. system allowed these 39 patients with unknown alcohol exposures to receive a diagnosis of FAS or PFAS because they presented with the Hoyme et al. FAS face. But the Hoyme et al. FAS facial criteria are so relaxed (specificity 71% to 75% [24, 25]) that the facial phenotype does not provide the necessary level of specificity to alcohol to use the facial phenotype to confirm exposure. Among the 39 patients with unknown prenatal alcohol exposure and a Hoyme et al. diagnosis of FAS or PFAS, 18 had relaxed PFLs (4^{th}–10^{th} percentile), 17 had relaxed philtrums (4-Digit Philtrum Ranks 2 and 3), 22 had relaxed lips (4-Digit Lip Ranks 1-3); 4 had no FAS facial features (4-Digit Face Rank 1); and 19 had only 1 FAS facial feature (4-Digit Face Rank 2).

Among the 834 patients that were classified "Not FASD" using the Hoyme et al. system, 31 received a FAS/PFAS diagnosis (Figure 10, red bars in the Hoyme et al. Not FASD row) using the 4-Digit Code. All 31 presented with the Hoyme et al. FAS face, but none met the Hoyme et al. FAS or PFAS diagnostic criteria. The Hoyme et al. FAS criteria require the presence of both CNS structural abnormalities (e.g., OFC ≤10th percentile) and neurobehavioral impairment. Eighteen presented with a small head circumference (OFC ≤10th percentile), but did not present with neurobehavioral impairment. All 18 were under 6 years of age. Of the 18 infants/toddlers, 5 were microcephalic (OFC ≤3rd percentile), but did not present with developmental delay ≥1.5 SD below the mean. All five were under 3 years of age and received the most severe FAS 4-Digit Code: 4444. Eight of the 31 presented with severe CNS dysfunction, but were normocephalic. Of the 29 with confirmed prenatal alcohol exposures, 5 had confirmed prenatal alcohol exposures, but the levels were reportedly too low to meet the Hoyme et al. alcohol exposure criteria.

The prevalence of each of the four core features that define FASD (growth deficiency, FAS facial phenotype, CNS abnormalities, and alcohol exposure) differed between the two diagnostic systems (Figure 11). Both systems identified 32% of patients with growth deficiency (height and/or weight ≤10^{th} percentile).

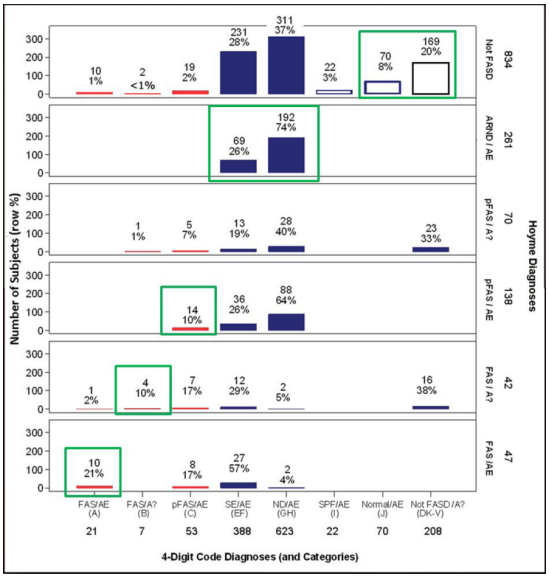

Figure 10. Cross-tabulation of the 4-Digit Code and Hoyme et al. FASD diagnostic outcomes.

Diagnostic concordance (green boxes) between the two systems was observed in 38% (528/1,392) of the patients. Diagnostic discordance (all diagnoses not outlined in green) was observed in 62% (864/1,392) of the patients. Red bars reflect FAS and PFAS diagnoses using the 4-Digit Code. As a demonstration for how to interpret this figure; 21 patients received a 4-Digit Code Diagnosis of FAS/AE. Of the 21 patients, 10 received a FAS/AE diagnosis, 1 received a FAS/A?, and 10 did not receive a diagnosis under the umbrella using the Hoyme et al. [3] diagnostic system. 4-Digit Code Categories A-V are case-defined in the Diagnostic Guide for FASD [1].

AE: alcohol exposed; A?: alcohol exposure unknown; ND: neurodevelopmental disorder; Not FASD/A?: Individuals who present with or without growth, facial, and/or CNS abnormalitities, but are not under the umbrella of FASD because their prenatal alcohol exposure is unknown and they do not meet the criteria for FAS/A?. SE: static encephalopathy; SPF: Sentinel Physical Findings, individuals who present with growth deficiency and/or 1 to 3 FAS facial features, but have normal CNS structure and function; Normal: no evidence of growth, facial, or CNS structural/functional abnormalites.

The Hoyme et al. system identified a higher proportion of patients (23%) with CNS structural/neurological abnormalities than the 4-Digit Code (17%). The higher prevalence with the Hoyme et al. system reflected the relaxation of the OFC criterion to the 10^{th} percentile. Both systems identified 1,219 (88%) with CNS dysfunction.

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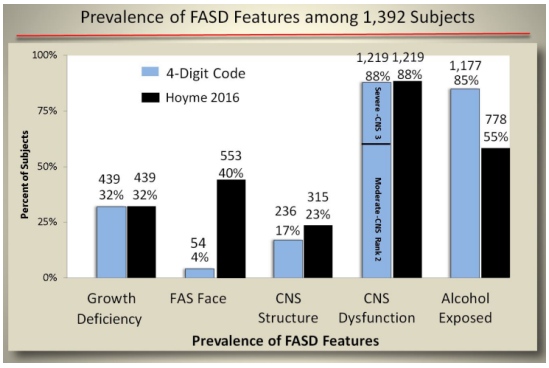

Figure 11. The prevalence of FASD features differed between the 4-Digit Code and Hoyme FASD diagnostic systems.

The prevalence of growth deficiency, the FAS facial phenotype, CNS abnormalities, and alcohol exposure differed when the two diagnostic systems were applied to the 1,392 patients. The most striking contrast is the 10-fold higher prevalence of the FAS facial phenotype with the Hoyme et al. criteria. Of the 1,219 with CNS dysfunction, the 4-Digit Code identified 828 (68%) with Rank 2 moderate CNS dysfunction and 391 (32%) with Rank 3 severe CNS dysfunction. The blue bars reflect the 4-Digit Code: (growth deficiency=Growth Ranks 2–4; FAS face=Face Rank 4; CNS structure=CNS Rank 4; Alcohol Exposed=Alcohol Ranks 3 and 4). CNS: central nervous system.

Of the 1,219 with CNS dysfunction, the 4-Digit Code identified 828 (68%) with Rank 2 moderate CNS dysfunction and 391 (32%) with Rank 3 severe CNS dysfunction. The prevalence of the FAS facial phenotype was 10-fold higher using the Hoyme et al. criteria (n=553; 40%) compared to the 4-Digit Code (n=54; 4%). Only 55% of the 1,392 patients met the more stringent Hoyme et al. alcohol exposure criteria. In contrast, 85% met the 4-Digit Code alcohol exposure criteria (Alcohol Rank 3 or 4).

The prevalence of the individual FAS facial features also differed between the two diagnostic systems (Figure 12). More patients were classified with short PFLs using the Hoyme et al. system (77% $\leq 10^{th}$ percentile) than the 4-Digit Code (59% $\leq 3^{rd}$ percentile). Three times more patients were classified with thin upper lips using the Hoyme et al. Lip/Philtrum Guide (64% with Lip Rank ≥ 4; lip circularity ≥ 52.5) compared to using the 4-Digit Code Lip-Philtrum Guide (23% with Lip Rank ≥ 4; lip circularity ≥ 75.5). The philtrums depicted on the two lip-philtrum guides appeared to be roughly equivalent resulting in both diagnostic systems identifying 20% of patients with Rank 4 or 5 smooth philtrums. The relaxation of the PFL and lip criteria in addition to requiring only 2 of the 3 facial features resulted in the Hoyme et al. criteria identifying 10 times more patients with the full Hoyme et al. FAS face (n=553, 40%) than the 4-Digit Code FAS face (Rank 4; n=54, 4%). The relaxation of the Hoyme et al. FAS facial criteria resulted in 71% (395/553) of the Hoyme et al. FAS faces to fall within the clinically normal range (Face Ranks 1 and 2) as defined by the 4-Digit Code (Figure 12B).

Cross tabulation of the CNS structural abnormalities and alcohol exposure classification document further contrasts between the two systems (Figure 13). Relaxation of the head circumference criteria in the Hoyme et al. system resulted in 315 patients with OFC $\leq 10^{th}$ percentile compared to 236 $\leq 3^{rd}$ percentile using the 4-Digit Code. The more stringent Hoyme et al. criteria for alcohol exposure resulted in substantially fewer patients being classified as alcohol exposed (n=778, 55%) compared to the 4-Digit Code (n=1,177, 85%). Most notably, 399 patients with confirmed alcohol exposures (Rank 3 and 4) did not meet the more stringent Hoyme et al. alcohol criteria because the requisite details of exposure were unknown (e.g., quantity, frequency, timing, BAC, etc.). When the details of the Hoyme et al. alcohol criteria are displayed, it becomes more clear which of these criteria are most likely not to be met or available to clinicians (Figure 14).

Objective 2c: Assess measures of validation

Correlation between the FAS facial phenotype and prenatal alcohol exposure:

If the FAS facial phenotype is specific to (caused only by) prenatal alcohol exposure, the FAS facial phenotype should be more prevalent among those with higher exposure and should not occur in individuals with confirmed absence of prenatal alcohol exposure. One would also expect that the majority of (if not all) individuals presenting with the FAS facial phenotype would meet criteria for a diagnosis under the umbrella of FASD.

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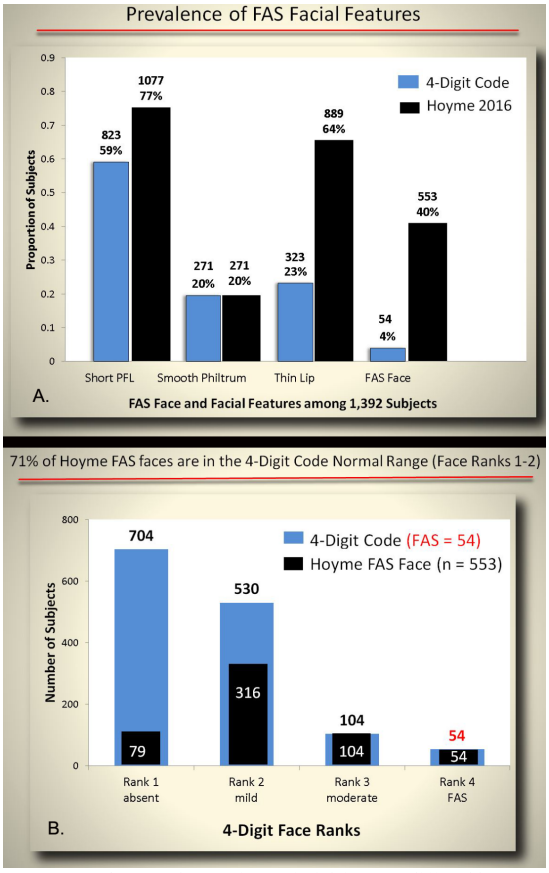

Figure 12. The prevalence of FAS facial features differed between the 4-Digit Code and Hoyme diagnostic systems.

A) When the facial criteria from each diagnostic system were applied to the 1,392 patients, the most striking contrast was the prevalence of the thin upper lip. Use of the Hoyme et al. North American Lip/Philtrum Guide resulted in 3 times more patients being classified as having a thin upper lip. The criteria used to define each bar: Short PFL (4-Digit Code $\leq 3^{rd}$ percentile; $\leq 10^{th}$ percentile Hoyme et al.); Smooth Philtrum and thin upper lip (Rank 4 or 5 on the 4-Digit Code or Hoyme et al. [3] lip philtrum guides); FAS Face (4-Digit Code Face Rank 4; Hoyme al. FAS/PFAS face). B) 71% of the Hoyme et al. FAS facial phenotypes fell in the 4-Digit Code normal range (Face Ranks 1 and 2).

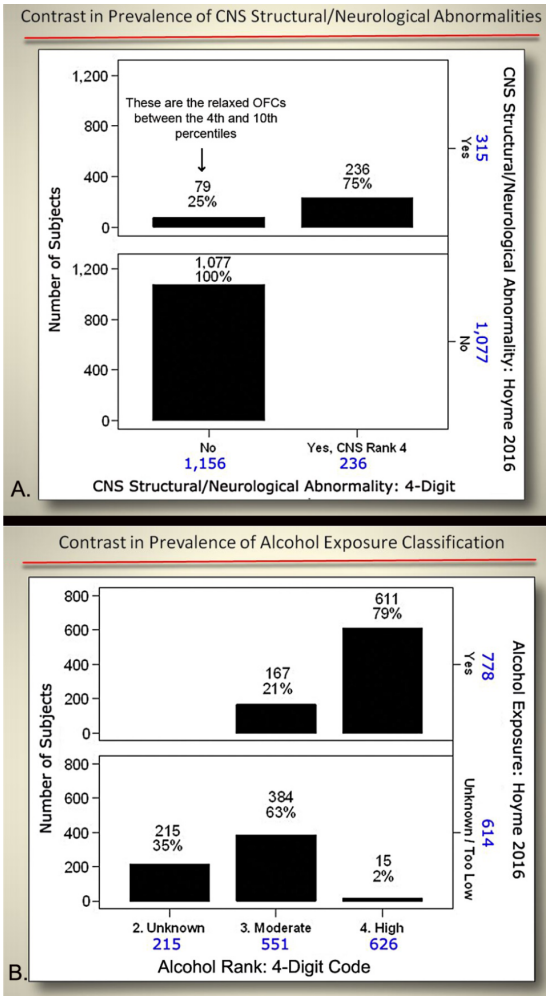

Figure 13. Cross-tabulation of CNS structural abnormalities and alcohol exposure classification between the 4-Digit Code and Hoyme systems.

To aid in interpretation; A) 315 patients met the Hoyme criteria for CNS structural/neurological abnormalities. Seventy-nine of the 315 did not meet the 4-Digit Code criteria for CNS Rank 4 because the head circumference was between the 4^{th} and 10^{th} percentiles. The 4-Digit Code requires a head circumference $\leq 3^{rd}$ percentile. B) 552 patients were classified as having moderate prenatal alcohol exposure using the 4-Digit Code (Alcohol Rank 3). Of the 551, only 167 met the Hoyme criteria of alcohol exposure. The remaining 384 had confirmed exposures, but details on quantity, frequency, timing, blood alcohol levels, etc. were not available to meet the more stringent Hoyme criteria. OFC: occipital frontal circumference.

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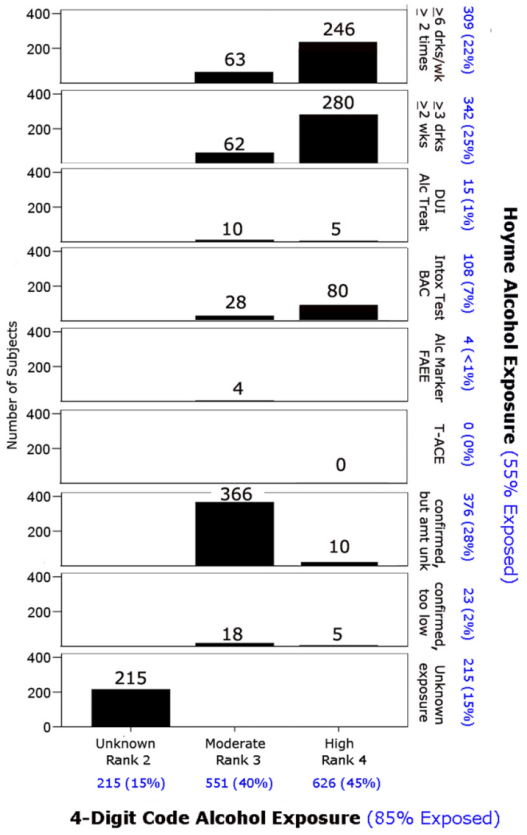

Figure 14. Cross-tabulation of the alcohol exposure classifications by the two 4-Digit Code and Hoyme diagnostic systems.

The Hoyme et al. alcohol exposure categories listed along the right border are fully defined in Table 2 published in the Hoyme et al. diagnostic guidelines [3]. Patients in this study were classified into only one of these categories starting with the top category (e.g., if a patient was exposed to ≥6 drinks/week ≥2 times and had a DUI, they were classified only in the ≥6 drinks/week ≥2 times category). Overall, 55% of the patients met the Hoyme alcohol criteria, whereas 85% met the 4-Digit Code alcohol criteria.

The 4-Digit Code Rank 4 FAS facial phenotype was significantly more prevalent among patients with higher prenatal alcohol exposure (Figure 15C, D). In contrast, the prevalence of the Hoyme et al. FAS facial phenotype was not more prevalent among patients with higher alcohol exposures. (Figure 15A, B).

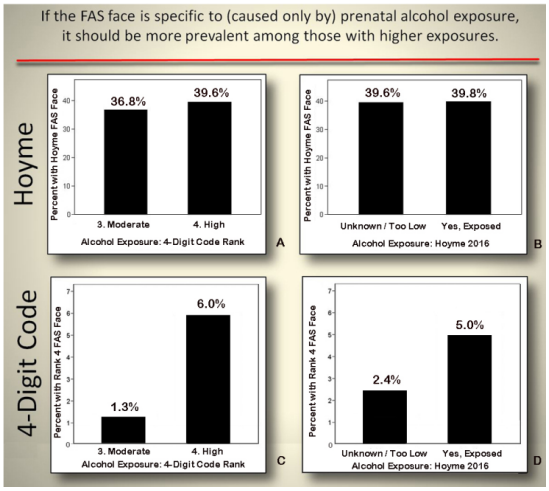

Figure 15. Only the 4-Digit Code FAS face was significantly more prevalent among patients with higher alcohol exposure.

A) The Hoyme et al. FAS face was equally prevalent and highly prevalent in the moderate (4-Digit Code Alcohol Rank 3) and high (4-Digit Code Alcohol Rank 4) alcohol exposure groups (Chi^2 0.9, p=0.33). B) The Hoyme et al. FAS face was also equally prevalent and highly prevalent between those that did and did not meet the Hoyme et al. alcohol exposure criteria (Chi^2 0.01, p=0.92). In contrast, the 4-Digit Code FAS facial phenotype was highly correlated with measures of prenatal alcohol exposure. C) The 4-Digit Code Rank 4 FAS face was 5 times more prevalent in the high exposure group (4-Digit Code Alcohol Rank 4) than the moderate exposure (Digit Code Alcohol Rank 3) group Chi^2 17.5, p=.000). D) The association between the 4-Digit Code Rank 4 FAS facial phenotype and alcohol was substantially weakened when the Hoyme et al. criteria for alcohol exposure were applied (Chi^2 6.1, p=0.02). The 4-Digit FAS face was only 2-fold more prevalent in the Hoyme et al. exposed group relative to the Hoyme et al. unknown/too low exposure group.

The mean number of days/week of drinking during pregnancy increased significantly with increasing magnitude of expression of the 4-Digit Code FAS facial phenotype (Figure 16A). The mean number of days/week of drinking during pregnancy was only marginally higher among those with the Hoyme et al. FAS facial phenotype, but this was driven largely by the inclusion of 65 patients who also met the more stringent 4-Digit Code FAS facial criteria (Figure 16B).

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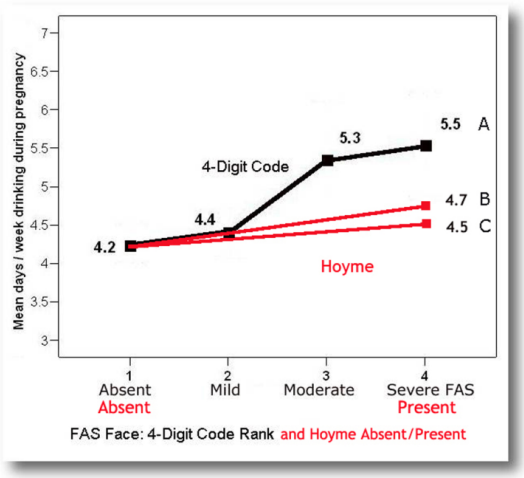

Figure 16. The 4-Digit FAS face was significantly associated with days/week of prenatal alcohol exposure.

A) A strong, significant, linear association was observed between the mean number of days/week of drinking during pregnancy and increasing magnitude of expression of the 4-Digit Code FAS facial phenotype (Face Rank 1 to 4) (One-way ANOVA Linear term: F=12.7, p=.000; n=615). Patients with the full Rank 4 FAS facial phenotype were exposed, on average, 1.3 more days per week than the patients with no FAS facial features (Face Rank 1). B) A much weaker, but significant, association was observed between alcohol exposure and the Hoyme et al. [3] FAS facial phenotype. Patients with the Hoyme et al. FAS face were exposed, on average, 0.5 more days per week than the patients without the Hoyme et al. FAS face (4.7 days/week vs 4.2 days/week respectively; T=-2.9, p=0.04). Sixty-five of the 242 patients with the Hoyme et al. FAS facial phenotype had moderate to severe FAS facial phenotypes in accordance with the 4-Digit Code (Face Ranks 3 and 4). C) When these 65 patients were removed from the analysis to assess the correlation between the relaxed Hoyme et al. facial criteria and prenatal alcohol exposure, patients with the relaxed Hoyme et al. FAS face were exposed, on average, only 0.3 more days per week than the patients without the Hoyme et al. FAS face; a difference that was no longer statistically significant (4.5 days/week vs 4.2 days/week; T=-1.4, p=0.16).

When these 65 patients were removed, there was no longer a significant contrast in alcohol exposure between those with and without the relaxed Hoyme FAS facial phenotype (Figure 16C).

When the Hoyme et al. and 4-Digit Code FAS facial criteria were applied to an adolescent with high function (FSIQ 123) and confirmed absence of prenatal alcohol exposure (4-Digit Code 1211), the adolescent met the Hoyme et al. criteria for the full FAS facial phenotype (Figure 6). In contrast, her facial phenotype was classified within the normal range by the 4-Digit Code (Face ABC-Score BBC, Face Rank 2).

Of the 553 patients with the Hoyme et al. FAS face, almost half (46%) did not receive a diagnosis under the umbrella of FASD using the Hoyme et al. system. In contrast, all 54 patients with the 4-Digit Code Rank 4 FAS face met criteria for a diagnosis under the umbrella of FASD using the 4-Digit Code.

Discussion

The FASD 4-Digit Code and Hoyme et al. 2016 FASD diagnostic systems produced markedly different outcomes. Only 38% of the 1,392 patients received concordant diagnoses from the two systems. Overall, the Hoyme et al. criteria rendered half as many diagnoses under the umbrella of FASD (n=558) as the 4-Digit Code (n=1,092) and placed a much higher proportion (53%; 297/558) in the FAS/PFAS categories than the 4-Digit Code (7%; 81/1,092).

Four factors accounted for the greatest contrasts in diagnostic outcomes between the two systems.

1. The more stringent Hoyme et al. alcohol exposure criteria prevented many with confirmed exposures from receiving a diagnosis of FASD. These more stringent criteria prevented almost one third (339; 29%) of the 1,177 patients with confirmed exposure from being able to receive a diagnosis under the umbrella of FASD (Figure 14). As we illustrated in Figure 9, individuals with *reported* prenatal alcohol exposures below the Hoyme et al. threshold can and do present with full FAS when using the 4-Digit Code. Either this patient was particularly vulnerable to the teratogenic impact of alcohol, or the *reported* exposure was not accurate. In a clinical setting, one is never in a position to know how accurate the exposure was recalled and reported. Setting a threshold implies the details of all reported exposures are accurate and no fetus can be harmed by exposures below the threshold. Neither statement is true and the latter sends a dangerous public health

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message that lower levels are safe. Recognizing this, the 4-Digit Code requires a confirmed exposure, but does not set a threshold.

It is interesting to note that Petryk et al., [26] reported similar findings when they retrospectively assessed the impact of applying the Canadian [2] minimal prenatal alcohol exposure thresholds to 119 patients with confirmed prenatal alcohol exposure (4-Digit Code Alcohol Ranks 3 or 4) and severe structural and/or functional CNS abnormalities (4-Digit Code CNS Ranks 3 and/or 4). The more stringent Canadian [2] exposure criteria would have prevented 71% of these individuals from receiving a diagnosis under the umbrella of FASD because the reported exposure would not have met the required threshold.

2. The Hoyme et al. criteria require both CNS structural and functional abnormalities be present to receive a diagnosis of FAS. Almost half of the patients who met the 4-Digit Code criteria for FAS did not meet the Hoyme et al. criteria for FAS because the patients were microcephalic, but too young (<5 years old) to engage in the types of testing needed to identify moderate or severe CNS dysfunction. The 4-Digit Code has confirmed that over 90% of alcohol-exposed infants and toddlers who present with one or more of the sentinel physical features of FAS as defined by the 4-Digit Code (microcephaly $\leq 3^{rd}$ percentile, a Rank 4 FAS facial phenotype, or Rank 4 growth deficiency) will present with severe CNS Rank 3 dysfunction later in childhood [5]. FAS is a birth defect syndrome, thus, by definition, it is present at birth. Failure to identify and diagnose FAS in newborns and infants will prevent these highest-risk children from receiving the benefits of early intervention. The 4-Digit Code allows evidence of CNS structural or functional abnormality to meet the CNS criteria. This allows FAS to be diagnosed in the newborn/infant who presents with the physical features (growth deficiency, the FAS facial features, and microcephaly), knowing these sentinel features are highly predictive of underlying CNS dysfunction that will manifest later in childhood.

3. The Hoyme et al. criteria prevent children under 3 years of age from receiving a diagnosis of ARND. As a result, 84% of the 87 alcohol-exposed infants/toddlers under 3 years of age that presented with moderate to severe CNS dysfunction and received a 4-Digit diagnosis of ND/AE or SE/AE (Figure 8C) did not receive a diagnosis anywhere under the umbrella of FASD using the Hoyme et al. system. Since ARND, by definition, is Neurodevelopmental Disorder caused by prenatal alcohol exposure, individuals with ARND are born with ARND. Failure to diagnose ARND in alcohol-exposed infants less than 3 years of age may prevent them from receiving the benefits of early intervention. The 4-Digit Code does not place age restrictions on any of the diagnoses under the umbrella of FASD.

4. The relaxation of the Hoyme et al. FAS facial phenotype criteria greatly increased the prevalence of FAS and PFAS diagnoses and threatened the validity of these FAS and PFAS diagnoses.

- The Hoyme et al. system classified 10 times more patients with the FAS facial phenotype (n=553) than the 4-Digit Code (n=54).
- The Hoyme et al. system produced 16 times more FAS/PFAS diagnoses with unknown alcohol exposure (n=112) than the 4-Digit Code (n=7). This is particularly concerning because 68 (61%) of these patients had 4-Digit Code Rank 1 or Rank 2 facial phenotypes that are, by our definition, clinically "normal". The Rank 1 and 2 phenotypes have no specificity to prenatal alcohol exposure [27]. The only reason FASD diagnostic systems allow a diagnosis of FAS to be made when prenatal alcohol exposure is unknown is because the facial phenotype is so highly specific to (caused only by) prenatal alcohol exposure, the face serves to confirm the exposure. If the facial phenotype defined by the diagnostic system is not confirmed to be highly specific to alcohol, then: 1) the diagnosis cannot be validly labeled FAS or PFAS because a causal link cannot be confirmed between the patient's alcohol exposure and their adverse outcomes, and 2) the facial phenotype cannot be validly used to confirm prenatal alcohol exposure when the history of exposure is unknown.

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- The 4-Digit Code allows a diagnosis of FAS to be made when prenatal alcohol exposure is unknown because the 4-Digit Code Rank 4 FAS facial phenotype is confirmed to be >95% specific to prenatal alcohol exposure [11, 28]. The 4-Digit Code does not allow a diagnosis of PFAS to be made when alcohol exposure is unknown, because the facial criteria for PFAS is relaxed to a Face Rank 3, resulting in a subtle reduction in specificity. To err on the conservative side, the 4-Digit Code requires a confirmed exposure for PFAS.
- In the current study the relaxed Hoyme et al. FAS facial phenotype demonstrated no association with prenatal alcohol exposure. In contrast, the 4-Digit Code FAS facial phenotype demonstrated a strong, significant, linear association with prenatal alcohol exposure.

- The Hoyme et al. system produced 4 times more FAS/PFAS diagnoses (297) overall than the 4-Digit Code (n=81).
- 70% of the 297 Hoyme et al. FAS/PFAS cases had "normal" 4-Digit Code Face Ranks 1 or 2.
- 46% of the 553 patients with the Hoyme et al. FAS face did not receive a diagnosis under the umbrella of FASD using the Hoyme et al. system. In contrast, all 54 patients with the 4-Digit Code Rank 4 FAS face met criteria for a diagnosis under the umbrella of FASD using the 4-Digit Code.

In addition to the contrasts in diagnostic criteria, the methods and tools used to measure the facial features are also markedly different. The authors of the Hoyme et al. system "*feel direct examinations of facial features are more practical in an office setting.*" The 4-Digit Code advises measuring the facial features from 2D digital photos using the FAS Facial Photographic Analysis Software [7]. Empirical studies have confirmed the superior accuracy of the photo versus direct method of facial measurement [8, 9]. Significant contrasts also exist between the 4-Digit Code Lip-Philtrum Guide 1 and the Hoyme et al. North American Lip/Philtrum Guide. As illustrated in Figure 2, although the Hoyme et al. North American Lip/Philtrum Guide looks similar in appearance to the 4 Digit Code Lip-Philtrum Guide 1, these are not interchangeable tools. The lips ranked 1 through 5 on the Hoyme et al. Guide do not match the lips ranked 1 through 5 on the 4-Digit Code Guide. The lips on the 4-Digit Code Guide become progressively thinner as Rank increases from 1 to 5. The lips on the Hoyme et al. guide do not become progressively thinner as Rank increases (e.g., the Hoyme et al. Rank 4 lip is thicker than the Hoyme et al. Rank 3 lip). The images used to depict lip thinness for each Rank do not match between the two guides. When the Hoyme et al. lips are mapped onto the 4-Digit Guide based on the objective measure of thinness (circularity), the Hoyme et al. Rank 1, 2, 3, 4, and 5 lips are equivalent to the 4-Digit Code Lip Ranks 2, 2, 3, 2, and 5, respectively. Both systems define the thin upper lip of FAS as Rank 4 or thinner. But the Hoyme et al. Rank 4 lip is substantially thicker than the 4-Digit Rank 4 lip (it is equivalent to the 4-Digit Rank 2 lip). The introduction of the Hoyme et al. North American Lip/Philtrum Guide serves to further relax the Hoyme et al. FAS facial phenotype. Only 2 of the 3 cardinal features are required and 2 of the 3 features are relaxed relative to the 4-Digit Code. The PFL is relaxed from the 3rd percentile to the 10th percentile and lip thinness is relaxed from Rank 4 to Rank 2 on the 4-Digit Code Lip-Philtrum Guide 1. An individual presenting with PFLs at the 10th percentile, a Rank 1 deeply grooved philtrum, and a 4-Digit Code Rank 2 moderately thick upper lip would meet the Hoyme et al. criteria for the full FAS facial phenotype. The presence of a single, very minor anomaly (PFL at the 10th percentile) does not constitute a dysmorphic facial phenotype. In fact, it would be difficult to justify classifying any of these three features as minor anomalies outside the normal range. Yet, this facial phenotype is used by the Hoyme et al. system to confirm prenatal alcohol exposure when prenatal alcohol exposure is unknown. Of the 71 patients with unknown prenatal alcohol exposure and the Hoyme et al. FAS facial phenotype, 70% had a 4-Digit Code Rank 1 or Rank 2 facial phenotype. By definition, 4-Digit Face Ranks 1 and 2 reflect normal phenotypes with no specificity to prenatal alcohol exposure. This was clearly illustrated in our FASD MRI study [27]. Sixteen high-functioning

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adolescents with confirmed absence of prenatal alcohol exposure were enrolled as controls in that study. Ten presented with Rank 1 facial phenotypes and 6 presented with Rank 2 facial phenotypes (one of which is illustrated in Figure 6). Based on the findings of the current study, the Hoyme et al. North American Lip/Philtrum Guide is not a valid tool for use with the 4-Digit Code. It is unfortunate and unclear why the Hoyme et al. system introduced a Lip-Philtrum Guide that emulates the 4-Digit Code Lip-Philtrum Guide (five images ranked 1 through 5 with Rank 4 identified as the clinical cut-off for the full FAS facial phenotype) when the Hoyme et al. FASD system only captures lip thinness and philtrum smoothness on a dichotomous (present/absent) scale. Only a single image (the Rank 4 image) is needed to classify the lip and philtrum as ≥Rank 4 on the Hoyme et al. North American Lip/Philtrum Guide. It is not clear why the tool includes Ranks 1, 2, 3 and 5 since none of these ranks or images are necessary to render Hoyme et al. FASD diagnoses.

Before leaving the topic of the FAS facial features, the presence/absence of a Cupid's bow warrants discussion. The Cupid's bow is the contour of the line formed by the vermilion border of the upper lip, resembling an archer's bow in the frontal view when a philtrum is present (Figure 17 A, B). Although the Hoyme et al.[3] diagnostic system clearly refers to the cardinal features of FAS as short palpebral fissures, smooth philtrum, and thin vermilion border of the upper lip and makes no reference to the Cupid's bow, Del Campo and Jones [29] suggest the Cupid's bow may be a more precise way to document a thin upper lip. Del Campo and Jones [29] describe a thin upper lip as follows, referencing the Hoyme et al. South African Mixed Race and North American White Lip/Philtrum Guides: "*A thin or narrow vermillion border of the upper lip has been considered another hallmark of the FAS since its initial definition. However many clinicians and investigators considered lack of the Cupid's bow shape of the upper lip as more precise in order to evaluate this feature as shown for scores 4 and 5 of the lip/philtrum guide*." The authors go on to report in the figure legend portraying the Lip/Philtrum Guides, "*For the vermillion border of the upper lip, the Cupid's bow shape is either lost (*Rank *5) or very underdeveloped (*Rank *4)*." While some in the field have referred to a thin upper lip as a thin vermilion border, it is not the border that is thin, it is the vermilion (or red) part of the upper lip that is thin. This red portion of the upper lip is more accurately referred to as the upper lip vermilion.

It is interesting to note that the although lip thinness on the Hoyme et al. North American Lip/Philtrum Guide does not increase linearly with increasing Rank as one would expect, the contour of the Cupid's bow does diminish linearly with increasing Lip Rank (Figure 2).

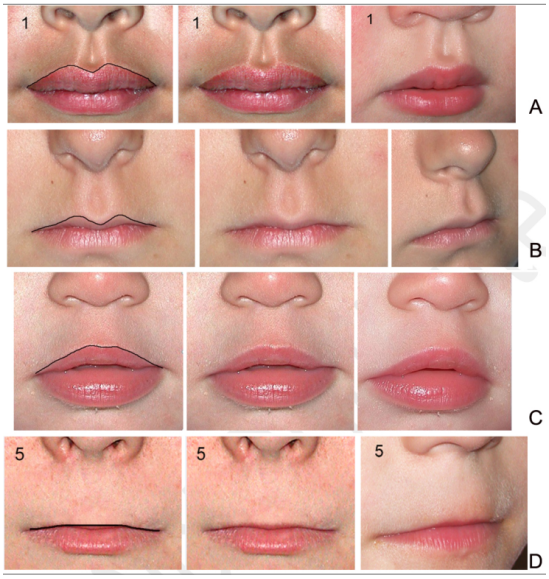

Figure 17. The absence of the Cupid's bow is not a more precise method for documenting a thin upper lip

The Cupid's bow (black line) is the contour of the line formed by the vermilion border of the upper lip, resembling an archer's bow in the frontal view. These images demonstrate that 1) the lower end of the philtrum groove and ridges form the Cupid's bow [30], and 2) the absence of the Cupid's bow is not a more precise method for documenting a thin upper lip [29]. The presence of a Cupid's bow is dependent on the depth of the philtrum, not the thinness of the upper lip. A deep philtrum will form a Cupid's bow even when the upper lip is thin. A and B) Examples of a deep philtrum creating a Cupid's bow in the contour of a thick and thin upper lip. C and D) Examples of a smooth philtrum failing to create a Cupid's bow in the contour of a thick and thin upper lip.

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Del Campo and Jones [29] appear to suggest that the lost or very underdeveloped Cupid's bow shape of the upper lip may be a more precise way to evaluate the thin upper lip feature.

We chose not to use the Hoyme et al. Lip/Philtrum Guide in this manner for the following reasons. First, the Hoyme et al. system makes no reference to the Cupid's bow as a cardinal feature of FAS. Second, the lack of a Cupid's bow reflects a smooth philtrum, not a thin upper lip. The Cupid's bow is formed by the philtrum intersecting with the vermilion border of the upper lip, thus the Cupid's bow is just another way of documenting the presence or absence of the philtrum (Figure 17). As defined by Hennekam et al. [30] in the Elements of Morphology, "*The philtrum is a vertical groove in the midline portion of the upper lip bordered by two lateral ridges or pillars It lies between the base of the nose (subnasale) and the vermilion border (labiale superius), which is also designated as the nasolabial distance. The lower end of the groove and the ridges form the central portion of the Cupid's bow of the vermilion."* And third, our dataset confirms that the absent or underdeveloped Cupid's bow depicted as Ranks 4 and 5 on the Hoyme et al. Lip/Philtrum Guide are not exclusively associated with Rank 4 or 5 thin upper lips. Individuals with thin upper lips present with distinct Cupid's bows when they have deep philtrums (Figure 17B) and individuals with thick upper lips have no Cupid's bow when they have smooth philtrums (Figure 17C). As stated in the Elements of Morphology [31], "*A thin upper lip vermilion may be associated with a smooth philtrum and an absence of the Cupid's bow, but these should be assessed separately."* In the absence of published validation studies supporting this proposed change in one of the cardinal facial features of FAS, clinical teams should adhere to the thin upper lip vermilion feature that is thoroughly validated [11, 28].

One anticipated critique of our use of lip circularity in this analysis is that Hoyme et al. may intend for their lip-philtrum guide to be used for in-person visual comparison, not for photographic analysis using an objective measurement of lip thinness. We considered using retrospective visual comparison with clinic photographs using the Hoyme lip-philtrum guide, but determined that since the lips on the Hoyme guide do not become progressively thinner as Rank increases, and there is some confusion as to whether lip thinness or flat Cupid's bow is being assessed with this guide, it would be too difficult to achieve adequate inter-rater reliability without relying upon the more objective measure of lip circularity.

The quintessential role of the FAS facial phenotype. Why are the criteria used to define the FAS facial phenotype so important to the medical validity of all diagnoses under the umbrella of FASD, not just the diagnosis of FAS? When one makes a diagnosis of FAS, one is stating explicitly that the individual has a syndrome caused by prenatal alcohol exposure [11]. One is also stating explicitly that the biological mother drank alcohol during pregnancy and, as a result, harmed her child. These are bold conclusions to draw and are not without medical, ethical, and even legal consequences. When the FAS face is not specific to FAS and prenatal alcohol exposure, the validity of the entire FASD diagnostic system collapses. Here is why.

- The term (FAS) is rendered invalid. If the face is NOT specific to (caused only by) alcohol, one can no longer label the condition fetal alcohol syndrome. One can no longer confirm alcohol is causally linked to any of the outcomes (growth, brain, or face) in an individual patient.
- The diagnosis (FAS with unknown alcohol exposure) is also rendered invalid. The FAS face can no longer serve as the confirmation of alcohol exposure when the exposure history is unknown.
- FAS is no longer distinct from ARND. ARND is essentially "FAS without the face." But if there is no FAS face, there is no distinction between FAS and ARND. Thus, one can no longer justify classifying FAS and ARND separately.
- The term "ARND" remains problematic. Since ARND has no feature specific to prenatal alcohol, one is in no position to declare the Neurodevelopmental Disorder is "Alcohol-Related" (ARND) in an individual patient.

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There are ethical consequences to the FASD diagnostic nomenclature. With a term like ARND, one feels compelled to require a significant exposure to alcohol to increase the odds that the individual's impairments may be caused, at least in part, by their alcohol exposure. This is a dangerous road to go down.

- Setting a threshold of significant exposure for ARND does not confirm the patient's alcohol exposure is related to their neurodevelopmental disorder.
- Alcohol is never the only risk factor contributing to the neurodevelopmental disorder. In this study population, 92% were exposed to other prenatal risks including poor prenatal care, pregnancy complications, and exposure to illicit drugs and tobacco. One percent presented with other syndromes (Down, Williams, Sticklers, etc.). Ninety-six percent experienced postnatal risks including trauma, neglect, multiple home placements, and physical/sexual abuse. Seventy-seven percent were in foster/adoptive care at the time of their FASD diagnosis. These other risk factors are so important in the differential diagnostic process, the 4-Digit Code Ranks the severity of these prenatal and postnatal factors on 4-point scales (just like it does for growth, face, CNS, and alcohol exposure) and reports them in full in the patient's medical record.
- One is sending a dangerous message that lower levels of alcohol exposure are safe. As we illustrated in Figure 9, individuals with reported prenatal alcohol exposures below the Hoyme et al. threshold do present with full FAS. Either this patient was particularly vulnerable to the teratogenic insult of alcohol, or the reported exposure was not accurate. In a clinical setting, one is never in a position to know how accurate the exposure is recalled and reported. Setting a threshold implies the details of all reported exposures are accurate and no fetus can be harmed by exposures below the threshold.
- And one is blaming a woman for harming her child, when they have limited ability to make/defend such a claim.

The 4-Digit Code introduced the terms ND/AE and SE/AE back in 1997 [14]. These terms state the verifiable facts; the individual presents with a disorder and the individual was exposed to prenatal alcohol exposure. The terminology does not explicitly state their disorder is related to their alcohol exposure. In fact, the 4-Digit Code formally Ranks all other prenatal and postnatal risks factors to make clear that alcohol is never the only risk factor contributing to an individual's neurobehavioral disorder of static encephalopathy. In 2013, the DSM5 [32] took a similar nosological approach when it introduced the new term "Neurobehavioral disorder associated with prenatal alcohol exposure" (ND/PAE) as a condition for further study.

- When is it a FASD? Fetal Alcohol Spectrum Disorders are, by definition, adverse outcomes caused by prenatal alcohol exposure. In the absence of an outcome that is specific to (caused only by) prenatal alcohol exposure (like the Rank 4 FAS facial phenotype), one cannot confirm or rule-out the role prenatal alcohol exposure played in an individual's CNS dysfunction. So…

- Do all individuals with SE/AE, ND/AE (or ARND) have FASD? Not necessarily. Only the subset of individuals whose CNS dysfunction was caused (in whole or in part) by their alcohol exposure has FASD.

- Which subset is that? We currently have no way of knowing. This is why the 4-Digit Code refers to SE/AE and ND/AE as 'broadly" under the umbrella of FASD. Those with SE and ND caused by their alcohol exposure have FASD. Those with SE and ND that was not caused by their alcohol exposure do not have FASD.

- But if they are exposed to high alcohol levels, can't we just assume alcohol caused their disability? No. Not everyone exposed to high levels of alcohol presents with adverse outcomes. Among 2,576 alcohol-exposed patients evaluated in the University of Washington FASDPN Clinic to date, 26 with high exposures presented with full FAS (4-Digit Codes 4444) while 41 with high exposures presented with normal growth, face, and brain development (4-Digit Codes 1114). We also see discordant outcomes among fraternal twins. Among

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20 twin pairs with identical high exposures, 5 had normal CNS function while their twin had moderate to severe CNS dysfunction.

When an individual presents with high alcohol exposure and severe CNS dysfunction, but no FAS facial phenotype, as depicted in the diagnosis SE/AE (4-Digit Code 2134):

- If their CNS dysfunction is caused (at least in part) by their alcohol exposure, then their SE/AE is an FASD.
- If their CNS dysfunction was caused by other risk factors, not their alcohol exposure, then their SE/AE is NOT an FASD.
- The only way we can link alcohol to an individual's CNS dysfunction is if they present with a highly specific Rank 4 FAS face (FAS 2434).

- If we cannot confirm alcohol caused their disabilities, does this impact our ability to provide them appropriate intervention? No. Intervention recommendations and a patient's access to services and supports should be based on their disabilities, not on what caused their disabilities. Twenty years of patient surveys [33] confirmed patients with a diagnosis of ND/AE and SE/AE were as likely to access and benefit from interventions as patients with FAS/PFAS. We did not have to label their disorder FAS or PFAS to qualify them for intervention and support services in Washington State.

- Does this impact our ability to prevent FASDs? No. To prevent FASD one must prevent prenatal alcohol exposure. To confirm efforts to prevent prenatal alcohol exposure are working, one needs to document prenatal alcohol exposure in a patient's medical record (regardless of outcome) and track the prevalence of prenatal alcohol exposure by birth cohort annually [34]. If one is reducing the prevalence of prenatal alcohol exposure, one is reducing the prevalence of FASD.

Sensitivity versus specificity

Hoyme et al. (3) reported *"Sensitivity and specificity are 2 sides of a diagnostic coin. Theoretically, the guidelines presented here* (the Hoyme et al. 2016 guidelines [3]) *demonstrating increased sensitivity could lead to over-diagnosis; thus, our advocacy for a structured expert multidisciplinary approach. On the other hand, strict diagnostic cutoffs associated with increased specificity could lead to under-diagnosis of affected children. Children with FASD are subject to a host of societal, educational, health, and judicial problems, all of which are affected by the time of diagnosis. Because early diagnosis and initiation of intervention should be of paramount importance, the authors assert that improved, sensitive, and inclusive diagnostic criteria for FASD should continue to be imperatives in the diagnostic process."* As demonstrated in the current study, strict diagnostic cutoffs (e.g., 3 facial features rather than 2, PFL 3rd percentile rather than 10th , lip Rank 4 rather than Rank 2; OFC 3rd percentile rather than 10th) associated with increased specificity did not lead to under-diagnosis of affected children when using the 4-Digit Code. The 4-Digit Code uses stringent cutoffs for the FAS facial phenotype to achieve diagnostic accuracy/validity. If the face is not specific to (caused only by) alcohol, one cannot validly label the condition FAS (or PFAS) because one cannot link the patient's adverse outcomes to their alcohol exposure. High specificity does not prevent individuals at risk for FASD from being identified and diagnosed. The 4-Digit Code is able to document the full continuum of outcomes and exposures (from 1113 to 4444) across the entire age span because it is not constrained by the implication of causation that comes with the term ARND. Aase and colleagues [35] urged "*simple recording of the verifiable conclusions. If prenatal alcohol exposure has taken place, but FAS cannot be substantiated, the exposure still should be indicated, and any nonspecific abnormalities or problems noted.*" This is the approach the FASD 4-Digit Code adopted when it was first introduced in 1997 [14]. This approach ensures no one is missed and no one is misdiagnosed.

The two diagnostic systems produce different outcomes, but which one, if either, is correct? Validation studies are required to confirm the accuracy, reproducibility, and medical validity of a diagnostic system. Validity is the degree to which a tool (or diagnostic system) is measuring what it

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purports to measure [36]. When the 4-Digit Code was introduced in 1997 [14, 16], it was published as an empirical study confirming its superior performance to the gestalt [37] approach it was designed to replace. Since then, two decades of more extensive laboratory, clinical, and public health empirical studies have comprehensively affirmed the validity of the FASD 4-Digit Code [11]. A clinician's guide for how to fully assess the performance of FASD diagnostic systems was introduced in 2013 [11] and replicated below (Table 2).

The guide proposes 12 questions clinicians should ask to assess the performance of FASD diagnostic systems. The 4-Digit Code's performance meets all 12 criteria. In contrast, the 2005 [38] and 2016 [3] versions of the Hoyme et al. FASD diagnostic systems were introduced without empirical studies confirming its superior performance to other published FASD systems.

The single most important form of validation required of a FASD diagnostic system is confirmation that the FAS facial phenotype is highly specific to (caused only by) prenatal alcohol exposure. As discussed above, in the absence of a highly specific facial phenotype, the validity of the entire FASD diagnostic system collapses. The labels FAS and PFAS are rendered invalid. Diagnoses of FAS and PFAS can no longer be validly rendered when prenatal alcohol exposure is unknown. And FAS and PFAS are no longer distinguishable from ARND. Several published studies have confirmed that the Rank 4 FAS facial phenotype is highly specific (>95% specificity) [11] to prenatal alcohol exposure while the Hoyme et al. FAS Facial phenotype has a reported level of specificity (71% to 75%) [24, 25] that is insufficient to confirm it is caused only by prenatal alcohol exposure. This absence of association between the Hoyme et al. FAS facial phenotype and prenatal alcohol exposure was further confirmed in the current study. To date, the FASD 4-Digit Code is the only FASD diagnostic system that has a published record of validation.

Table 2. As clinicians assess the performance of FASD diagnostic guidelines, clinicians should ask the following questions [11]

1. Have properly designed studies been published to confirm the case definition for the FAS facial phenotype is highly specific (>95%) to FAS and alcohol (e.g. observed only among individuals with prenatal alcohol exposure and FAS)? If the FAS facial phenotype is not highly specific to prenatal alcohol exposure, FAS cannot be diagnosed when prenatal alcohol exposure is unknown.
2. Was data used to empirically derive the diagnostic guidelines? Was the data drawn from a large, representative, population-base?
3. Has the performance of the guidelines been empirically assessed (validated)?
4. Individuals are born with FAS/D. Can the diagnostic system identify FAS/D at birth and across the lifespan?
5. Growth deficiency, the FAS facial phenotype, CNS abnormalities, and alcohol exposure all present along clinically meaningful continuums. The FAS facial phenotype is not just present or absent. The brain is not just normal or abnormal. Do the Guidelines recognize/incorporate these important continuums?
6. Do the guidelines produce clinically distinct subgroups across the full spectrum (FAS, PFAS, SE/AE, ND/AE)?
A. Do brain imaging studies identify statistically significant contrasts between the FASD subgroups?
B. Individuals with FAS have more severe CNS dysfunction than individuals with "ARND". Do the Guidelines generate FAS and "ARND" groups that demonstrate this important contrast?
C. Do individuals who meet the criteria for FAS actually have FAS?
7. Can the guidelines detect unique alcohol exposure patterns between the FASD subgroups?
8. Can the diagnostic system be effectively and efficiently taught to interdisciplinary teams?
9. Are the guidelines confirmed to be reproducible? If two clinics use the guidelines, do they render the same diagnoses?
10. Do families report high satisfaction/confidence with the diagnostic process/outcome?
11. Are the names of the diagnoses (FAS, PFAS, SE/AE, ND/AE) medically valid? Do they imply causality between alcohol and outcome that cannot be confirmed in the individual patient?
12. Do diagnoses under the umbrella of FASD qualify patients for intervention services that lead to improved outcomes?

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Conclusions

The FASD 4-Digit Code and Hoyme et al. 2016 FASD diagnostic systems produced markedly different outcomes. Only 38% of the 1,392 patients received concordant diagnoses from the two systems. Overall, the Hoyme et al. criteria rendered half as many diagnoses under the umbrella of FASD as the 4-Digit Code (558 and 1,092 respectively) due to more stringent alcohol exposure criteria and the setting of minimum age restrictions. The Hoyme et al. criteria placed a much higher proportion of FASD diagnoses in the FAS and PFAS categories than the 4-Digit Code (53% and 7%, respectively) because of the substantial relaxation of the Hoyme et al. FAS facial phenotype criteria. The Hoyme et al., FAS/PFAS facial phenotype had no correlation with or specificity to prenatal alcohol exposure. In contrast, the 4-Digit Code Rank 4 FAS facial phenotype was highly correlated with and highly specific to prenatal alcohol exposure. The Hoyme et al. North American Lip/Philtrum Guide and 4-Digit Code Lip-Philtrum Guide 1, while similar in appearance, are not equivalent tools. The Rank 4 moderately thin upper lip on the Hoyme et al. Guide is equivalent to the Rank 2 moderately thick upper lip on the 4-Digit Guide. The FASD 4-Digit Code has been extensively validated [11] over the past 20 years. In contrast, the relaxation of the FAS facial phenotype criteria poses a major threat to the validity of the Hoyme et al. 2016 FASD diagnostic system.

Ethical approval

This study was approved by the University of Washington Human Subjects Division.

Author contribution

All authors are members of the interdisciplinary FASD diagnostic team and participated in the interpretation and reporting of the study's outcomes. SJA conducted the statistical analyses.

Guarantor: Susan J. Astley

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ARTICLE

An investigation of intra-individual variability in children with fetal alcohol spectrum disorder (FASD)

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ABSTRACT

Intra-individual variability (IIV) is defined as systematic within-person variation in performance either across test sessions (e.g., test/retest performance on the same task) or in one session (e.g., variations in performance on multiple trials of a single task). Higher levels of IIV have been noted as a characteristic of neurodevelopmental disorders such as attention deficit/hyperactivity disorder (ADHD), but IIV is yet to be investigated in fetal alcohol spectrum disorder (FASD). FASD is a term used to describe a range of conditions resulting from prenatal exposure to alcohol. As part of a comprehensive neuropsychological battery, four study groups (1. fetal alcohol syndrome/partial fetal alcohol syndrome; 2. static encephalopathy/alcohol exposed; 3. neurobehavioral disorder/alcohol exposed as diagnosed using the University of Washington FASD 4-Digit Code; 4. typically-developing (TD) age-matched children with no prenatal alcohol exposure) were administered measures of motor response and inhibitory control, attention, and adaptive behavior. The results indicate increased levels of IIV in those with FASD compared to the TD controls. It was found that IIV uniquely contributes to predicting adaptive behavior above and beyond attention, while attention partially mediates the relationship between IIV and adaptive behavior. This is the first study to the authors' knowledge to show the presence of increased IIV in children with FASD. It additionally provides evidence that IIV measures some inherent variability in performance independent of poor attention in children with FASD.

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Fetal alcohol spectrum disorder (FASD) is a broad nonclinical term used to describe several conditions resulting from prenatal exposure to alcohol. FASD has been documented as occurring worldwide and according to Roozen et al. (2016), the prevalence of FASD per 1000 live births in the United States (US) is estimated to be 0.7 for fetal alcohol syndrome (FAS), 2.2 for partial fetal alcohol syndrome (pFAS), 9.1 for alcohol-related neurodevelopmental disorder (ARND), and 2.6 for alcohol-related birth defects (ARBD). Other diagnostic criteria and terminology have been developed for children

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with prenatal exposure to alcohol; for example, in Canada "FASD" can now be used as a diagnostic term with specifiers (Cook et al., 2016), rather than a nonclinical umbrella term. This lack of universal criteria and terminology means that children can be given different diagnoses depending on the criteria used. It should be noted that this paper uses terms that are consistent with the University of Washington FASD 4-Digit Code, a case-defined, validated system that characterizes a pattern of growth deficiency, facial dysmorphology, central nervous system (CNS) functional and structural abnormalities, and prenatal alcohol exposure (Astley, 2013). This system derives four diagnoses under the umbrella of FASD: FAS, pFAS, static encephalopathy/alcohol exposed (SE/AE), and neurobehavioral disorder/alcohol exposed (ND/AE). There has been an increasing amount of research conducted on the cause and symptoms of children with FASD—however, the research is still in the early stages of facilitating a clear understanding of the widespread effects of prenatal exposure to alcohol (for reviews, see Guerri, Bazinet, & Riley, 2009; Kable et al., 2016; Mukherjee, 2015). In order to expand the current understanding of the behavioral outcomes of children with FASD, this paper investigates intra-individual variability (IIV) and its relationship with attention and adaptive behavior in children with FASD.

The individual symptoms seen in those with FASD differ depending on circumstances such as the amount of alcohol consumed by the mother, nutrition, maternal age, stage of gestation, etc. (May et al., 2013; Sulik, 2005); therefore, not all symptoms are present in every case, and those that are vary in their degree of severity (Astley, 2013).

Individuals diagnosed with FASD frequently exhibit considerable within-group variability in the presentation of symptoms and are clinically noted to exhibit higher levels of variation in the performance of academic and daily activities when compared to typically-developing (TD) children. For example, variability seen in social communication has been rationalized as being due to children with FASD having deficits in attention and executive function, leading to hyperactivity and a lack of awareness of the displeasure of their peers (Kjellmer & Olswang, 2012; for a review, see Mattson, Crocker, & Nguyen, 2011). Variability has also been seen in motor response times; Simmons, Thomas, Levy, and Riley (2010) found that as the planning demands of a motor task increased, so did the within-group variability and length of response times of their FAS group compared with their control and prenatal alcohol exposed (PAE) groups. There was no difference found between the FASD groups and control group when the response planning required was minimal, suggesting that the variability in performance in individuals with FASD increases with cognitive demand.

Although considerable information about the variability *between* individuals with FASD has been noted, as far as the authors' are aware, to date there have been no studies investigating task performance response variability *within* individuals with FASD—that is, what has been termed IIV, which is defined as systematic within-person variation in performance either across testing sessions (e.g., test/retest performance on the same task) or on a single session (e.g., variations in performance on multiple trials of a single task). Compared to between-person variability, the measurement of IIV adds information related to the consistency or stability of performance over time (where high IIV implies low consistency). This type of variability, though not formally measured in children with FASD, has been noted as a common feature of the disorder. A case study by Timler and Olswang (2001) investigated an

8-year-old boy diagnosed with FAS to determine discrepancies between parent and teacher determinations of the best educational program for him, noting that "behavior was inconsistent from day to day" (Timler & Olswang, 2001, p. 51) and that this was not due to intentional disobedience. Similar statements can be found from support forums where parents and guardians of children with FASD report this inexplicable IIV in their children ranging from social interactions to academic performance. Many forums and information booklets describe these inconsistencies in performance as the child having "on" and "off" days. Malbin (2004) states that inconsistencies in memory or performance are a primary feature of children with FASD and that this is reflective of the functioning of underlying brain structures. Kjellmer and Olswang (2012) further note that children with FASD exhibit higher levels of variability in social communication, elaborating that these inconsistencies in communication make interactions with these children unpredictable—especially when they perform similarly to their TD peers on some days but not on others. A number of studies have documented greater within-participant variability in reaction times—i.e., reaction time *SD* (RTSD)—on sustained attention tasks in children with prenatal alcohol exposure (Olson, Feldman, Streissguth, Sampson, & Bookstein, 1998; Streissguth, Barr, Sampson, and Parrish-Johnson, 1986; Streissguth, Bookstein, Sampson, & Barr, 1995; Streissguth et al., 1994), a finding replicated in studies of animals prenatally exposed to alcohol (Hausknecht et al., 2005).

Intra-individual Variability (IIV)

IIV is defined as a within-person variation in performance either across testing occasions—such as the variability measured for a single person on a single task across multiple sessions spanning the short term (trials) to the long term (days, weeks, etc.)—or in a single session—variability for a single person at a single occasion across multiple trials (MacDonald & Stawski, 2014). Whereas some level of variability is typical due to practice and fatigue effects, when the variability seen is not a random occurrence but becomes trait-like and characteristic of an individual's performance then it is of clinical interest. It should be noted that a distinction is made between systematic and permanent changes over time, often referred to as intra-individual change (Nesselroade, 1991), and reversible changes over short periods of time. For the purpose of this paper, IIV is used to mean the latter definition.

IIV appears to be a sensitive predictor of neural dysfunction. An overall increase in IIV has been documented as occurring in clinical groups with cognitive difficulties, including aging populations (Dykiert, Der, Starr, & Deary, 2012), those with traumatic brain injury (Hill, Rohling, Boettcher, & Meyers, 2013; Stuss, Murphy, Binns, & Alexander, 2003), individuals with dementia (MacDonald, Nyberg, & Bäckman, 2006), and children with attention deficit/hyperactivity disorder (ADHD) and other neurodevelopmental disorders (Geurts et al., 2008). The study of IIV in aging and traumatic brain injury populations is of interest, as it may shed light on the possible changes in neural structures that can account for this variability in performance. Similarly, it is also of interest when studying young children with neurodevelopmental disorders to understand variations in the abilities of these children compared to their TD peers.

IIV is not a consistent aspect of the neural system, but rather appears to have a developmental trajectory. In their review of IIV, MacDonald et al. (2006) discuss the U-shaped function of IIV over the life span – in general, IIV is higher in early childhood, begins to decrease into adolescence and adulthood as the neural system becomes more efficient during the natural pruning and myelination processes, and then begins to increase again in later adulthood, which is associated with lower efficiency and cognitive decline. Given this connection between a decrease in IIV and synaptic pruning, as this process is compromised in children with prenatal alcohol exposure (Lebel et al., 2012; Treit et al., 2013) it is possible that the IIV seen in FASD may be higher than in TD children. Lebel et al. (2012) found that in children with FASD, cortical loss over time is positively related to the amount of alcohol exposure prenatally. Specifically, they found that those with FASD did not have increases in cortical volume *before* synaptic pruning began; these increases are seen in TD controls. They suggest that these trajectories indicate a lack of plasticity, so that when pruning occurs during later years, those with FASD may actually be losing important neural connections, thereby decreasing cognitive efficiency (Lebel et al., 2012).

While there are a number of structural central nervous system symptoms associated with FASD (for reviews, see Moore, Migliorini, Infante, & Riley, 2014; Wilhelm & Guizzetti, 2015), Treit et al. (2013) investigated abnormalities in the white matter tracts of children with FASD using diffusion tensor imaging (DTI). Two measures used in DTI are fractional anisotropy (FA), which measures the direction of proton diffusion, and mean diffusivity (MD), which measures the magnitude of diffusion. As children typically mature, so too do their white matter connections in the brain, allowing for more efficient conduction and a decrease in variability; therefore, in DTI, maturation is associated with an increase in FA and a decrease in MD. Treit et al. (2013) notes that during development, the FASD group showed some expected changes in white matter (increased FA and decreased MD) but not to the degree of the controls, especially in the frontal regions of the brain, suggesting poor myelination as a possible explanation. As IIV is often conceptualized as a metric for efficiency in the neural connections, these findings can be extrapolated to suggest an increase in variability in the FASD group, along with lower efficiency. Indeed, Tamnes, Fjell, Westlye, Ostby, and Walhovd (2012) report a decrease in IIV from childhood into adolescence, rationalized as secondary to improved white matter connectivity and maturity. Research has also found evidence supporting differences in more central regions while using DTI to investigate the integrity of white matter connections in the brain of TD children (Tamnes et al., 2012) and those with FASD (Treit et al., 2013). A recent review by Wilhelm and Guizzetti (2015) consolidates research detailing the negative effect of prenatal exposure to alcohol on glial cells that play an essential role in CNS structural development including myelination and plasticity, which may account for the widespread effect of the teratogen on brain development.

IIV and Attention

As measures of IIV are typically calculated on tasks that require some level of sustained attention over repeated trials (e.g., continuous performance tasks, go/no-go tasks, etc.), it is important to understand the relationship between IIV and aspects of attention. Kelly, Uddin, Biswal, Castellanos, and Milham (2008) investigated two competing networks with regard to IIV and attention in healthy participants: the "task-positive"

network that becomes active during a task and is related to attention, and the "task-negative" network that is deactivated during a task but active at rest, also known as the default mode network (DMN). They found that as the negative correlation between the two networks increases, the variability in performance decreases, meaning that performance stabilizes as more attention is given to the task. However, when both these networks are activated and therefore competing with each other, the variability of performance increases, especially as the task becomes more complex. This suggests that as attention becomes more compromised, so (too) does the response to the stimuli. This provides a possible mechanism whereby disorders affecting attention networks may also be associated with increased variability in performance.

Although research similar to that of Kelly et al. (2008) has not been conducted on an FASD population, there have been resting-state studies investigating the DMN in this population. Specifically, Santhanam et al. (2011) investigated the DMN of adults with prenatal alcohol exposure compared to controls and found, using a resting-state functional magnetic resonance imaging (fMRI), that the level of deactivation in the DMN was lower for the alcohol-exposed group than for the controls. The DMN is more active during rest, so change is measured in levels of deactivation. Based on the findings of Kelly et al. (2008), less deactivation implies increased competition with the task-positive network. Santhanam et al. (2011) similarly suggest that the lower levels of deactivation seen in the clinical groups implies that there is some competition (attentional modulation) between the DMN and cognitive activity, resulting in dysfunctional or poorer performance in the clinical groups. Castellanos, Kelly, and Milham (2009) describe a similar relation between the DMN and IIV in children with ADHD.

There has also been some research conducted on IIV in children with ADHD, a common comorbid diagnosis with FASD, and a population where within-person *variability* in performance is considered by some researchers to be a *stable* between-person characteristic of the disorder (see Castellanos & Tannock, 2002). Additionally, Gmehlin et al. (2014) investigated attention and inhibition in a population of non-medicated adults with ADHD using IIV and errors of commission and omission on a go/no-go task. They argued that their findings of increased IIV and errors of omission suggest deficits in sustained attention—that disruptions in sustained attention that do not ultimately result in errors of omission instead lead to longer response times—and secondarily increased IIV.

Research by Geurts et al. (2008) argues that variability in performance is not specific to ADHD, as their findings support increased IIV in children with high-functioning autism (HFA), with comorbid autism spectrum disorder (ASD) and ADHD, as opposed to those with ADHD alone or TD children. They support their findings with the argument that previous studies have not controlled for comorbidity in their participants; this conclusion is also echoed by studies investigating similar responses in children with HFA, ADHD, and Tourette's syndrome (Verté, Geurts, Roeyers, Oosterlaan, & Sergeant, 2006).

IIV and Adaptive Behavior

Burton, Strauss, Hultsch, and Hunter (2009) investigated the relationship between IIV and everyday problem-solving in older adults. They point out that everyday problem-solving is an ecologically valid way of measuring an individual's abilities (as opposed to IQ), and determined that those with more inconsistent reaction times

(that is, higher IIV) have poorer everyday problem-solving abilities, thereby suggesting that the IIV measure has some "functional" relevance. Additionally, studies have pointed to the link between the frontal lobes and adaptive behavior (Schoenbaum, Roesch, Stalnaker, & Takahashi, 2009), as well as the frontal lobes and IIV (Bellgrove, Hester, & Garavan, 2004; MacDonald et al., 2006; Simmonds et al., 2007), thus suggesting a relationship between IIV and adaptive behavior. However, it should be noted that although Burton et al. (2009) highlight that everyday problem-solving is a more ecologically valid way of measuring ability than IQ, a relationship between the two constructs does exist. This is not surprising given the overlap in these constructs, and definitions of IQ such as "intelligence is the aggregate or global capacity of the individual to act purposefully, to think rationally and to *deal effectively with his environment*" (Wechsler, 1944, p. 3). Indeed, IQ is typically found to be predictive of adaptive behavior in children with developmental disorders, especially in lower-functioning groups (Bölte & Poustka, 2002; Duncan & Bishop, 2013; Liss et al., 2001).

Children with FASD have also been documented as exhibiting deficits in adaptive behavior when compared to controls on communication, daily living skills, and socialization domains (Crocker, Vaurio, Riley, & Mattson, 2009; Jirikowic, Kartin, & Olson, 2008; Rasmussen, Andrew, Zwaigenbaum, & Tough, 2008) and these deficits are significantly more impaired than in children with ADHD. Crocker et al. (2009) highlight that even though there are shared symptoms between children with ADHD and those with FASD, the latter are more impaired on daily living skills, and while children with ADHD tend to improve with age, such a relation is not seen in those with FASD, suggesting an "arrest" in development in these skills versus a "delay" (Crocker et al., 2009, p. 22).

Aim and Hypothesis

The current study aims to investigate IIV in children with FASD compared to TD controls with no prenatal exposure to alcohol. Based on the existing literature, children with FASD are anticipated to have higher levels of IIV when compared to controls. The relationship between IIV and attention has been outlined in previous studies (e.g., Kelly et al., 2008) as well as the relationship between attention and adaptive behavior (e.g., Clark, Prior, & Kinsella, 2002), and between IIV and adaptive behavior (e.g., Burton et al., 2009). These relationships also lead to the question of how, and if, the assessment of IIV provides any information that is distinct from the assessment of attention, for example in relation to behavioral outcomes such as accounting for adaptive behavior. In other words, is IIV a unique or sensitive measure in an FASD population, as has been proposed in older populations (Hultsch, Strauss, Hunter, & MacDonald, 2008)? As such, this study also aims to investigate the relationship between IIV, attention, and adaptive behavior: specifically, it was hypothesized that IIV would account for additional variability in adaptive behavior independent of attention. Finally, it was hypothesized that attention would be found to mediate the relationship between IIV and adaptive behavior.

Method

Participants

The protocol was approved by the University of Washington Human Subjects Review Board. The individuals involved in this study were participants in the FASD MRI/MRS (magnetic resonance spectroscopy)/fMRI study conducted by Astley and colleagues in 2007 (Astley, Aylward, et al., 2009a, 2009b; Astley, Olson, et al., 2009; Astley, Richards, et al., 2009). Three FASD groups were chosen from 1200 patients who were previously diagnosed by an interdisciplinary team in the WA State FAS Diagnostic & Prevention Network (FAS DPN) or clinics using the FASD 4-Digit Code (Astley, 2013, 2004).

The first group, FAS/pFAS (n = 20), is comprised of children with severe cognitive/behavioral dysfunction and/or CNS structural/neurological abnormalities, and the FAS facial phenotype. These groups were combined because the primary clinical difference between FAS and pFAS is the presence of growth deficiency in the former. The second group, SE/AE (n = 24), is comprised of children with severe cognitive/behavioral dysfunction and/or CNS structural/neurological abnormalities, but without the FAS facial phenotype (the main distinguishing feature from group 1). The FASD 4-Digit Code defines severe cognitive/behavioral dysfunction as three or more domains of function (e.g., cognition, memory, language, etc.) that are two or more *SD*s below the mean based on standardized psychometric tools administered by clinicians. The 4-Digit Code ranks severe dysfunction as CNS Rank 3. CNS structural/neurological abnormalities may include microcephaly, structural abnormalities detected on MRI, and/or a seizure disorder. These structural/neurological abnormalities are assigned a CNS Rank 4. The third clinical group, ND/AE (n = 21), is comprised of children with prenatal alcohol exposure and moderate cognitive/behavioral dysfunction. The children in this group did not present with CNS structural/neurological abnormalities or the FAS facial phenotype. Moderate dysfunction is defined by the FASD 4-Digit Code as cognitive/behavioral function or development that is impaired but insufficient to receive a CNS Rank 3 classification. Moderate dysfunction is classified as CNS Rank 2. The fourth group, TD controls (n = 16), is comprised of children with no prenatal alcohol exposure who were healthy and did not present with academic concerns. They were chosen from a large cohort of children who, at birth, were enrolled in a University of Washington study of typical development conducted via the Department of Speech and Hearing Sciences. This registry of children has been maintained over the years to serve as a source of healthy controls for studies conducted across the university.

The children in all four groups were balanced on age (within 6 months), gender, and race. See Table 1 for demographic information and Astley et al. (2009b) and Astley, Olson, et al. (2009) for additional neuropsychological profile data not used in the current study.

IIV Measurement

While there are multiple ways of measuring IIV, including simple measures of intra-subject variability such as the intra-individual coefficient of variation (ICV) and the

Table 1. Demographic Profiles and Performance on Measures of IQ, Attention and Adaptive Behavior.

	Group			
	FAS/pFAS	SE/AE	ND/AE	Control
Characteristics	*n* = 20	*n* = 24	*n* = 21	*n* = 16
Female, *n* (%)	10 (50.0)	8 (33.3)	10 (47.6)	8 (50.0)
Age (years), *M* (*SD*)	12.7 (2.4)	12.2 (2.0)	12.4 (2.3)	12.4 (2.7)
Race, *n* (%)				
Caucasian	12 (60.0)	11 (45.8)	12 (57.1)	13 (81.3)
African American	6 (30.0)	4 (16.7)	6 (28.6)	2 (12.6)
Native American	2 (10.0)	7 (29.2)	2 (9.5)	0 (0.0)
Other	0 (0.0)	2 (8.3)	1 (4.8)	1 (6.3)
FSIQ[1]*, *M* (*SD*)	77.5 (14.4)	79.3 (10.5)	99.2 (11.3)	123.9 (6.5)
Attention[2]*, *M* (*SD*)	59.8 (20.1)	70.9 (22.9)	81.9 (24.7)	103.6 (15.5)
Adaptive Behavior[3]*, *M* (*SD*)	59.0 (17.5)	55.0 (14.2)	65.4 (21.1)	95.3 (12.3)

Note. *Standard score: *M* = 100, *SD* = 15; [1]Wechsler Intelligence Scale for Children – Third Edition (WISC-III; Wechsler, 1991); [2]Full-Scale Attention Quotient, Integrated Visual and Auditory Continuous Performance Test; [3]Adaptive Behavior Composite, Vineland Adaptive Behavior Scales – Interview Format. FAS/pFAS = fetal alcohol syndrome/partial fetal alcohol syndrome; ND/AE = neurobehavioral disorder/alcohol exposed; SE/AE = static encephalopathy/alcohol exposed.

raw-score intra-individual *SD* (raw-score ISD), in the current study the IIV is calculated using a residual ISD method (Bielak, Hultsch, Strauss, MacDonald, & Hunter, 2010; Geurts et al., 2008; Hultsch et al., 2008). In their discussion of methods of calculating IIV using measurements of reaction times (RTs) to simple motor tasks, Hultsch et al. (2008) state that this ISD method provides information about either the amount of IIV (analyses investigating short-term variability in behavior) or the form of the IIV (analyses aimed at investigating systematic changes over time); the present study seeks to examine the *amount* of IIV. For the "amount" calculations, Hultsch et al. (2008) describe residual ISD (among others) as a preferred method. The residual ISD method (see the Statistical Procedures section below) for calculating IIV on RT involves saving residual scores for the RT of each individual trial (unpredictable variation) following a regression partialing out confounding variables (e.g., mean RT, systematic time-based effects related to practice or learning), thus leaving only unsystematic trial-to-trial variation. The within-person, across-trial *SD* of these residual values is known as the residual ISD (Geurts et al., 2008; Hultsch et al., 2008).

Hultsch et al. (2008) highlight the advantages of using the residual ISD method over the raw-score ISD for the calculation of IIV. One benefit of the residual ISD is that it accounts for the correlation typically observed between the intra-individual mean and the raw-score ISD. For example, unlike the raw-score ISD method, which may be impacted by between-group variations in performance (e.g., group differences in mean RT), the residual ISD method adjusts for between-group differences in mean RT with linear regression, eliminating this as a potential source of bias. Secondly, residual ISD also allows IIV scores to be adjusted for differences due to systematic within-person variation (variation due to a known mechanism), such as from the effects of fatigue or practice; this is the rationale for including trial sequence as a predictor in the regression model. In summary, residual ISD can be thought of as a "purer" and therefore more construct-valid measure of IIV than raw-score ISD. While raw-score ISD reflects both unsystematic and systematic trial-to-trial variations in RT, residual ISD reflects only that within-person variation in RT which is not systematically related to linear change across trials or to group

differences in mean RT. The raw score ISD does not adequately capture the phenomenon of interest (seemingly random fluctuations in RT across trials) because it does not isolate unsystematic variance from that which is systematic (i.e., related to differences across trials or between groups).

IIV Tasks

All participants completed two tasks (Letters Game & Arrows Game) aimed at assessing unique components of inhibitory control during a task requiring sustained attention. These tasks include a control continuous performance condition (typically simple detection of a stimulus) and an inhibitory condition (requiring participants to attend to salient but irrelevant stimuli). Specifically, in the Letters Game (a go/no-go paradigm), in the control condition single capital letters appear on a computer screen and the participants are required to hit the space bar for the "X" trials. In the inhibitory condition, the participants hit the space bar for all letters except "X", that is, they are asked to inhibit the response when "X" is on-screen (Figure 1(a)). In the Arrows Game (a game requiring overcoming prepotent motor response), an arrow appears on-screen requiring participants to either push the arrow key pointing in the same direction (control condition) or the opposite direction (inhibitory condition) as the displayed arrow (Figure 1(b)).

Attention Task

All participants completed the Integrated Visual and Auditory (IVA; Tinius, 2003) continuous performance test (CPT). The IVA CPT is a standardized go/no-go-type

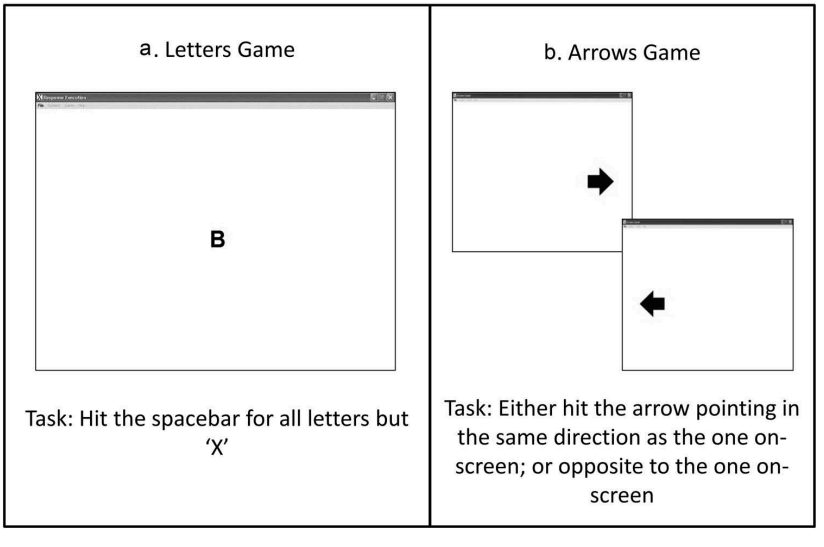

Figure 1. Screenshots of a task for (a) the Letters Game and (b) the Arrows Game.

computerized test that simultaneously assesses both visual and auditory aspects of attention, providing measures of vigilance, focus, and speed. During the task, participants either see or hear the numbers "1" and "2". They are then expected to respond by clicking a button or mouse when a "1" is seen or heard and to inhibit that response when a "2" is seen or heard. This measure thus produces separate scores for visual and auditory attention that are combined into a "full-scale attention quotient". For the purposes of this study, the full-scale attention quotient is used in the analyses (see Table 1; additional IVA scores are published in Astley, Olson, et al., 2009).

Adaptive Behavior Measure

The Vineland Adaptive Behavior Scales – Interview Format (VABS; Sparrow, Balla, & Cicchetti, 1984) was completed by a parent or guardian of each participant. Adaptive behavior represents the typical performance of an individual—that is, it is meant to assess what an individual actually does, behaviorally, on a daily basis. The VABS is a standardized age-based parent questionnaire containing statements that are rated as *usually*, *sometimes*, or *never* based on the target individual's abilities. The statements fall into three major domains (Communication, Daily Living Skills, and Socialization) that combine into the overall Adaptive Behavior Composite that is used in the present analyses (see Table 1; additional VABS scores are published in Astley, Olson, et al., 2009). The VABS is a common measure that is used to assess an individual's deficits in adaptive functioning in order to assist in diagnosis (such as intellectual disability or ASD), to understand the impact of a diagnosis, or to advise intervention planning, since it is deemed to be directly applicable to the skills that an individual will use in daily living (Cicchetti, Carter, & Gray, 2013).

Statistical Procedures

Preparation.

The data for each task (the Letters Game and the Arrows Game) were analyzed separately for ease of operation. They were firstly prepared by removing participants where there are missing data due to equipment failure or incomplete tasks. As a result, one participant from the SE/AE group was removed from the Arrows Game, while no participants were removed from the Letters Game analyses. As is standard for the calculation of IIV, implausible outliers in the response times were removed, such as extremely fast responses (less than 150 ms, generally indicative of anticipatory errors). Extremely slow responses are thought to be due to distraction from the task and were also removed for the calculation of IIV. These upper boundaries for slow responses were computed separately for each task; the games differ in presumed complexity and therefore it is thought that the mean RT for each task will reflect this. The upper boundary for each task was equated to the mean RT for the task plus three times its *SD*. The removal of these outliers in the RTs allows for a more conservative estimation of IIV. In total, for the Letters Game approximately 4% of trials were removed, while 2% were removed for the Arrows Game.

Intra-Individual Variability (IIV).

IIV was indexed by computing ISDs (see Bielak et al., 2010). The ISD represents the variability of each individual's RT across the individual task trials. Separate ISDs were

computed for each condition (control and inhibition) within each task. Because the means and *SD*s of raw RTs are correlated within persons, the ISD method involves saving the residuals from a regression to partial out effects of possible confounding variables (including trial, condition, and group) to parse the unique variance of each individual. This residual was then converted to a standardized *t*-score ($M = 50$, $SD \approx 10$) to allow for comparison across tasks. The final IIV measure is the *SD* across the trials of these *t*-scores, which is the ISD per individual, per condition, per task.

Results

Mean Reaction Times (RTs)

A mixed analysis of variance (ANOVA) was undertaken to compare the main effects of group (between-subjects variable) and condition (within-subjects variable), as well as to determine if an interaction exists between group and condition. For both the Letters Game and the Arrows Game, an investigation of the mean RT between groups for each condition indicated a main effect of condition where, as expected, the mean RT of the inhibition condition, $F(1, 77) = 49.44$, $p < .001$, partial $\eta^2 = .39$, is significantly slower than the control condition, $F(1, 76) = 28.23$, $p < .001$, partial $\eta^2 = .27$.

A main effect for group is also present for the Letters Game, $F(3, 77) = 3.36$, $p < .05$, partial $\eta^2 = .12$, and the Arrows Game, $F(3, 76) = 5.03$, $p < .01$, partial $\eta^2 = .17$. There is no significant interaction effect. Significant group differences were further explored via the Duncan post hoc test that essentially identifies which group means differ (see Table 2 for mean values and Duncan post hoc groupings).

IIV

IIV estimates per task per condition were compared using a mixed ANOVA to examine the main effects of group and condition and their interaction. Investigation of the IIV for the Letters Game revealed main effects for both group, $F(3, 77) = 4.33$, $p < .01$, partial $\eta^2 = .14$, and condition, $F(1, 77) = 52.51$, $p < .001$, partial $\eta^2 = .41$. No significant interaction effect was found. The variability in the inhibition condition was higher than that of the control condition across all groups (see Table 2).

Table 2. Means for Reaction Times (RTs) and IIV.

		Letters Game			Arrows Game		
Group	Condition	*n*	RT (ms)	IIV	*n*	RT (ms)	IIV
FAS/pFAS	Control	20	385.275	6.263	20	537.366	7.963
(1)	Inhibition		437.828	10.163		651.772	8.453
SE/AE	Control	24	434.738	7.624	23	516.719	9.263
(2)	Inhibition		480.838	11.806		628.128	9.618
ND/AE	Control	21	393.475	6.399	21	456.592	5.764
(3)	Inhibition		447.009	10.337		543.288	6.485
Control	Control	16	367.744	4.560	16	383.491	5.400
(4)	Inhibition		404.654	7.052		439.032	5.483
Duncan Post Hoc Tests			134, 123	123, 4		123, 34	12, 134

Note. FAS/pFAS = fetal alcohol syndrome/partial fetal alcohol syndrome; ND/AE = neurobehavioral disorder/alcohol exposed; SE/AE = static encephalopathy/alcohol exposed.

Investigation of the IIV for the Arrows Game revealed a main effect for group, $F(3, 76) = 2.90$, $p < .05$, partial $\eta^2 = .10$. There is no significant main effect for condition, nor is there an interaction effect (see Table 2).

Attention and Adaptive Behavior

A one-way ANOVA revealed significant differences between group performance on attention measures, $F(3, 76) = 13.39$, $p < .001$, $\eta^2 = .35$, and adaptive behavior measures, $F(3, 75) = 21.12$, $p < .001$, $\eta^2 = .46$.

IIV, Attention, and Adaptive Behavior

Hierarchical regression was utilized to analyze the relationship between these variables, specifically whether IIV accounts for more variation in adaptive behavior above and beyond attention. The total attention quotient was entered into the first block, followed by the IIV for the Letters Game. This specific IIV score was chosen due to the simplicity of the Letters Game task, thus resulting in a pure baseline measure of IIV.

A hierarchical regression for the full sample was completed. The results indicate an overall significant regression, $F(2, 77) = 12.66$, $p < .001$, where attention and IIV together account for 25.2% of the variance in adaptive behavior. Attention significantly accounts for 16.8% of the variance in adaptive behavior, while IIV significantly accounts for an additional 8.4% of variance in adaptive behavior (see Table 3). Alternatively, entering IIV into the hierarchical regression first results in it significantly accounting for 15.0% of the variance in adaptive behavior, while attention significantly accounts for 10.3% of the variance above and beyond the IIV. This suggests that there is a shared variance between IIV and attention (approximately 6%), as well as unique contributions, with regard to predicting adaptive behavior.

An additional hierarchical regression analysis was carried out where IQ was controlled by entering it into the equation first, followed by attention, then IIV. The results indicate a significant regression model, $F(3, 77) = 25.61$, $p < .001$, where overall 50.9% of the variance in adaptive behavior is accounted for by IQ, attention, and IIV. Interestingly, after IQ is entered, attention and IIV no longer account for any unique significant variation in adaptive behavior. Specifically, IQ accounts for 49.1% of the variance in adaptive behavior in this model (see Table 3).

Table 3. Hierarchical Regression Analyses for Adaptive Behavior.

Variable	β	R^2 change	F change
Model 1			
Attention	0.332	0.168**	15.389
IIV	−0.300	0.084*	8.430
Model 2			
IIV	−0.300	0.150**	13.392
Attention	0.332	0.103*	10.294
Model 3			
IQ	0.622	0.491**	73.349
Attention	0.051	0.003	0.426
IIV	−0.135	0.015	2.314

Note. *Correlation significant at the .01 level (two-tailed); **Correlation significant at the .001 level (two-tailed).

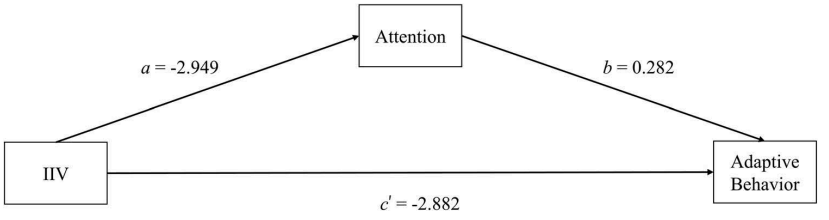

Figure 2. Simple mediation model of the direct and indirect effects of IIV on adaptive behavior.

Table 4. Model Outcomes for Test of Mediation: Does Attention Mediate the Relationship between IIV and Adaptive Behavior?

		Consequent						
		Attention				Adaptive Behavior		
Antecedent		Coefficient	*SE*	*p*		Coefficient	*SE*	*p*
IIV	*a*	−2.949	1.249	<.05	*c′*	−2.882	0.993	<.01
Attention		—	—	—	*b*	0.282	0.088	<.01
		R^2 = .068				R^2 = .252		
		$F(1, 76) = 5.573$, $p < .05$				$F(2, 75) = 12.662$, $p < .001$		

Mediation Analysis

A simple mediation analysis was carried out using ordinary least-squares path analysis. The results indicate that IIV indirectly affects levels of adaptive behavior through its effect on levels of attention. As noted in Figure 2 and Table 4, IIV has a negative effect on attention levels ($a = -2.949$), while attention levels have a positive effect on adaptive behavior ($b = 0.282$). A bias-corrected bootstrap confidence interval for the indirect effect of IIV on adaptive behavior through its effect on attention ($ab = -0.832$), based on 10,000 bootstrap samples, does not include zero (−2.021 to −0.096), thus indicating a significant indirect effect. There is also evidence that IIV influences adaptive behavior independent of its effect through impacting attention ($c' = -2.882$).

Discussion

The present study investigates the mean RT and IIV of three distinct groups of children with FASD (FAS/pFAS, SE/AE, and ND/AE) and one control group comprised of TD children with no prenatal alcohol exposure, using two different tasks. Mean RT and IIV were calculated for each task, group, and condition. The results indicate that overall, the control group was both faster and had lower IIV than the FASD groups.

As expected, the mean RT for the inhibition condition of each task was found to be significantly higher, meaning that the participants responded more slowly when alternating between an activation and inhibition task. This finding is consistent with this condition, as it is more challenging—even if only slightly—than the control condition. The differences in mean RT between groups, across trials and tasks, are reflective of the control group being significantly faster than the FASD groups. Additionally, similar to the

report of Simmons et al. (2010), the overall RT of both the clinical and control groups increases as the difficulty of the task increases, secondary to the greater cognitive processing required for response planning. For this study, not only is the mean RT of both tasks higher on average in the inhibition condition for each group, but it is higher overall for the Arrows Game, which requires the participant to decide between two differing motor responses (consistent with differences seen in simple versus choice reaction times; Simmons et al., 2010). Simmons et al. (2010) suggest that for children with FASD, the additional RT increase in motor tasks that require a response selection (such as the Arrows Game) may be due to alcohol-related changes affecting the CNS (related to planning time) and peripheral nervous system (related to motor response time).

It is well established that children tend to be more variable in cognitive performance when compared to adolescents and adults (MacDonald et al., 2006). The present findings on IIV suggest that children on the fetal alcohol spectrum tend to be even more variable than their age-matched TD peers on a go/no-go paradigm requiring a motor response. The higher IIV in the clinical groups compared to the controls possibly adds to the understanding of how prenatal exposure to alcohol can affect the developmental trajectory of the brain. The IIV findings indicate group effects for both tasks where the control group is typically less variable. Whereas Simmons et al. (2010) report that as the cognitive demands of a task increase so does the response variability within an FASD group, the present findings take this a step further in their indication that as the cognitive demand increases so too does the variability *within* an individual with FASD IIV. The present findings are consistent with those of Geurts et al. (2008), who note that both the mean RT and IIV of their clinical populations were higher than those of the controls. Visual inspection of the IIV data in the present study also reveals that within the clinical groups, the SE/AE group had on average the highest level of IIV compared to the FAS/pFAS and ND/AE groups.

To the authors' knowledge, this is the first study to investigate IIV in individuals with FASD, but it is by no means the only neurodevelopmental disorder with this feature; similar findings have been reported in children with ADHD, ASD, and Tourette's syndrome (Geurts et al., 2008; Verté et al., 2006). This leads to the question of whether the IIV noted in these populations is any different; that is, is the IIV seen in children with FASD any different from that of children with ADHD, or even those with co-morbid diagnoses, and is it possible to distinguish between these groups based on their levels of variability? This is an area that clearly requires further investigation.

A common conclusion in the literature is that IIV is reflective of the integrity of brain structures and may additionally be due to competition between the DMN and the task-oriented network in other populations (Castellanos et al., 2009; Kelly et al., 2008). Although the DMN in those with FASD has been investigated (e.g., Santhanam et al., 2011), there has yet to be a direct comparison with levels of IIV in this population. Additionally, the negative impact of alcohol on the developing brain includes impairments in neuronal migration (e.g., Guerri et al., 2009; Wilhelm & Guizzetti, 2015) and synaptic pruning (e.g., Lebel et al., 2012; Treit et al., 2013), to name a few. Impairment in these neurodevelopmental processes may additionally contribute to the expression of IIV in this population.

In order to investigate the clinical utility of IIV compared to attention, analyses were carried out to determine whether IIV accounts for variability in adaptive behavior

above and beyond that due to poor attention. With regard to IIV, attention, and adaptive behavior, the initial regression results across all groups indicate that attention and IIV together account for 25.2% of the variance in adaptive behavior. Attention and IIV share approximately 6% of this variance, while they also contribute uniquely. Specifically, IIV accounts for an additional 8.4% of the variance in adaptive behavior after the variance accounted for by attention and the shared variance between attention and IIV (totaling 16.8%) is removed, suggesting that IIV does in fact measure something different than basic attention deficits and is not simply a result of poor attention. While it has been suggested that attention and IIV are related (Gmehlin et al., 2014; Kelly et al., 2008), the present findings also highlight a unique contribution from each to real-life functioning, as assessed by an adaptive behavior measure. This finding is similar to that reported by Burton et al. (2009) in an aging population, where higher IIV was determined to be a useful predictor of activities of daily living. If the RT IIV is related to disruptions in underlying neural processes (e.g., Kelly et al., 2008) then it can similarly lead to inconsistency in activities of everyday living (e.g., Timler & Olswang, 2001) reflected as lower levels of adaptive behavior.

On the other hand, previous studies have highlighted the predictive power of IQ regarding adaptive behavior (Bölte & Poustka, 2002; Duncan & Bishop, 2013; Liss et al., 2001). In the present study, when the impact of IQ on adaptive behavior is controlled (regressed out), neither attention nor IIV account for additional variance in adaptive behavior. Therefore, while IIV and attention have unique contributions when predicting adaptive behavior, it appears that IQ remains the best predictor. This may not be surprising given the overlap between these latter two constructs. The focus of adaptive behavior tests is on the measurement of abilities such as being able to cope with environmental changes, learn new everyday skills and demonstrate independence, which to some extent likely overlap with the ability to "deal effectively with the environment" as assessed by IQ. Regressing IQ onto adaptive behavior first would indeed remove the "shared" aspects of adaptive behavior and intellectual ability, perhaps the variability that is most related to IIV and attention. Indeed, Dennis et al. (2009) state that statistically covarying or controlling for a demographic trait that is relevant to and characteristic of a group is misleading and often provides anomalous and counterintuitive findings. In addition, the lack of meaningful relationship between IIV and adaptive behavior when IQ is controlled does not suggest that there is no utility to understanding the role of IIV as it relates to processes such as attention. In fact, IIV has been noted to anticipate the onset and trajectory of changes in the cognitive performance in an aging population (Bielak et al., 2010) and may be useful in predicting the same in a younger population. Additionally, it may be worthwhile to investigate whether the role of IIV in predicting adaptive behavior is different in an aging FASD population.

A simple mediation analysis was undertaken to further explore the relationship between IIV and attention when predicting adaptive behavior. Both direct and indirect relationships were found where IIV directly accounts for variance in adaptive behavior and also indirectly accounts for variance in adaptive behavior through its influence on attention. While attention does not fully mediate the relationship between IIV and adaptive behavior, it does play a partial role in the relationship (Figure 2). For this analysis, the assumption was that IIV precedes both attention and adaptive behavior in time—that is, IIV influences attention. While some researchers discuss IIV as a result of

impaired attention (Kelly et al., 2008), evidence of IIV being associated with developmental disorders such as ADHD (Castellanos & Tannock, 2002; Gmehlin et al., 2014) and aging (MacDonald et al., 2006) suggests that it may be due to a lack of development or breakdown of processes that are more basic than levels of attention, and may be a cause rather than an outcome of poor attention.

Limitations and Future Directions

Along with the possible directions outlined throughout the discussion, it would be of worth to investigate the trajectory of IIV in children with FASD over time. It has previously been mentioned that IIV in a TD population presents in the form of a U-shaped curve over the life span (for a review, see MacDonald et al., 2006). The question remains as to whether a similar decrease in IIV is seen in children with FASD when they approach adolescence and adulthood, and additionally whether the difference in variability compared to TD individuals will hold, which it is hypothesized—based on the findings in the present study—is likely.

Assessing longitudinally the outcome of a targeted intervention in clinical groups with varying levels of IIV would add more information with regard to the benefits of measuring IIV early on, especially for an age group where IQ testing is unavailable or unfeasible (e.g., younger than 6 years of age, or impaired language). As children become older their requirements and demands for daily living increase, which is where there tends to be a departure of clinical groups from TD children (Crocker et al., 2009). If there is additional differentiation in this adaptive behavior between groups with varying levels of IIV it may prove useful in determining the level of care required. Finally, other studies investigating IIV have looked at neural and cognitive correlates (e.g., Bellgrove et al., 2004), and this is a proposed future direction for this clinical population.

Another important issue to consider is the fact that children with FASD tend to have higher levels of environmental instability, such as an increased number of placements in foster care (Streissguth et al., 2004), and this likely has an effect on brain development. As a result, this environmental instability, in addition to the teratogenic effects of alcohol, may contribute to the varying levels of IIV seen in clinical populations. Conversely, due to an unclear cause and effect relationship, high levels of IIV in these children may present an additional challenge when providing care resulting in frequent changes to their living environment. While the current study does not investigate specific contributors to IIV, this may be a future direction worthy of investigation.

A limitation of the current study is that IIV is measured from the motor RT of a basic task that is reflective of a continuous performance test of attention that indeed is similar to the way in which the measure of attention was administered. As a result, future investigations of IIV in this population may benefit from using an RT measure that is not as closely tied to measures of attention. Secondly, after cognitive testing, the control group was found to have cognitive abilities that are in the above average range, which may not represent the population of TD children; however, this may also be the result of excluding participants from the control group if there was any uncertainty of alcohol being consumed prenatally. Thirdly, due to the low sample size of each group, regression analyses were undertaken for all participants and the study lacked sufficient power for looking at whether the impact of IIV in

each group was similar. Additionally, a cause and effect relationship cannot be guaranteed based on the simple mediation analyses carried out in this study, which include specific variables that do not rule out the possible impact of other unmeasured variables. Finally, the correlation found between the variables measured is dependent on the reliability of those measures—that is, how accurately they measure the true score.

Conclusion

The results of this study are the first to demonstrate an increased level of IIV in children with FASD compared to TD children, and add further information on the effect of prenatal exposure to alcohol. It is additionally established that IIV does contribute uniquely above and beyond attention when predicting the variance in daily adaptive behaviors, and that attention acts as a partial mediator between IIV and adaptive behavior.

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Research Article

Listening Difficulties in Children With Fetal Alcohol Spectrum Disorders: More Than a Problem of Audibility

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Purpose: Data from standardized caregiver questionnaires indicate that children with fetal alcohol spectrum disorders (FASDs) frequently exhibit atypical auditory behaviors, including reduced responsivity to spoken stimuli. Another body of evidence suggests that prenatal alcohol exposure may result in auditory dysfunction involving loss of audibility (i.e., hearing loss) and/or impaired processing of clearly audible, "suprathreshold" sounds necessary for sound-in-noise listening. Yet, the nexus between atypical auditory behavior and underlying auditory dysfunction in children with FASDs remains largely unexplored.
Method: To investigate atypical auditory behaviors in FASDs and explore their potential physiological bases, we examined clinical data from 325 children diagnosed with FASDs at the University of Washington using the FASD 4-Digit Diagnostic Code. Atypical behaviors reported on the "auditory filtering" domain of the Short Sensory Profile were assessed to document their prevalence across FASD diagnoses and explore their relationship to reported hearing loss and/or central nervous system measures of cognition, attention, and language function that may indicate suprathreshold processing deficits.
Results: Atypical auditory behavior was reported among 80% of children with FASDs, a prevalence that did not vary by FASD diagnostic severity or hearing status but was positively correlated with attention-deficit/hyperactivity disorder. In contrast, hearing loss was documented in the clinical records of 40% of children with fetal alcohol syndrome (FAS; a diagnosis on the fetal alcohol spectrum characterized by central nervous system dysfunction, facial dysmorphia, and growth deficiency), 16-fold more prevalent than for those with less severe FASDs (2.4%). Reported hearing loss was significantly associated with physical features characteristic of FAS.
Conclusion: Children with FAS but not other FASDs may be at a particular risk for hearing loss. However, listening difficulties in the absence of hearing loss—presumably related to suprathreshold processing deficits—are prevalent across the entire fetal alcohol spectrum. The nature and impact of both listening difficulties and hearing loss in FASDs warrant further investigation.

Fetal alcohol spectrum disorder (FASD) is an umbrella term used to describe the range of physical, functional, and neurological abnormalities caused by prenatal alcohol exposure. It has been estimated that FASDs affect at least 1% of children and perhaps more (Sampson et al., 1997), with prevalence estimates varying by geographic location and diagnostic methodology (Roozen et al., 2016). Among all FASDs, fetal alcohol syndrome (FAS) is the most visibly evident diagnosis, characterized by growth deficiency and a specific set of facial features (i.e., thin upper lip, smooth philtrum, and small eyes), in the presence of significant central nervous system (CNS) abnormality (Astley, 2004, 2013; Bertrand et al., 2005). However, the majority of people with an FASD lack these observable physical markers yet still experience a wide and variable range of functional impairments. These typically include learning, attention, impulse control, communication, and social skill deficits (Astley, 2004; Kodituwakku & Kodituwakku, 2014; Streissguth et al., 2004; Thorne, 2017).

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A small body of classic literature suggests that the teratogenic effects of prenatal alcohol exposure may involve insults to the auditory system potentially resulting in hearing loss (i.e., decreased sensitivity to low-level sound) and/or "suprathreshold" deficits affecting the processing of clearly audible sound essential for picking out sound targets in noise. A complex hierarchy of suprathreshold processing operations originating in the CNS and the auditory periphery is involved in separating out and making sense of the myriad acoustic signals generated by competing sound sources. Key mechanisms include the extraction of spatial information and precise encoding of the spectrotemporal features unique to each sound source, perceptual separation of sound streams and formation of distinct "auditory objects," and selective attention to the target auditory object (reviewed in Bizley & Cohen, 2013; Carlyon, 2004; Griffiths & Warren, 2004; B. C. J. Moore & Gockel, 2012; Shinn-Cunningham, 2008, 2017; Shinn-Cunningham, Best, & Lee, 2017). Suprathreshold processing deficits can arise, for example, as a consequence of inadequate sensory encoding (e.g., broad frequency tuning on the basilar membrane [Kortlang, Mauermann, & Ewert, 2016] or temporal coding infidelities [Bharadwaj, Masud, Mehraei, Verhulst, & Shinn-Cunningham, 2015]), binaural/spatial processing deficits (Ross, Fujioka, Tremblay, & Picton, 2007), or impaired cognitive control processes (e.g., attention deployment) in the absence of auditory coding deficits (Lee, Larson, Maddox, & Shinn-Cunningham, 2014). Damage to these or other suprathreshold processes can compromise sound-in-noise listening abilities and—like hearing loss—can impact daily function (Hillock-Dunn, Taylor, Buss, & Leibold, 2015; Shinn-Cunningham, 2017). Such auditory dysfunction may contribute significantly to some of the communication impairments observed in FASDs. In the complex acoustic environments common to daily life (e.g., classrooms, restaurants), both hearing loss and suprathreshold listening deficits in the absence of hearing loss have the capacity to negatively impact speech perception (reviewed in Bronkhorst, 2015). Such degradation of the speech signal may limit the auditory information children rely on to decipher and learn fundamental linguistic rules (White-Schwoch et al., 2015).

In terms of processes associated with audibility, impairments in mechanisms and structures involved in detecting low-level sound have been observed in individuals with FAS and in laboratory animals with extensive prenatal alcohol exposure. Prenatally exposed rats were found to have significantly prolonged and/or reduced-amplitude auditory brainstem responses and damaged hair cell receptors indicative of sensorineural (inner ear/auditory nerve) hearing loss (Church et al., 1987; Church & Kaltenbach, 1997). Consistent with this, hearing loss of both sensorineural and conductive (middle ear) origin has been shown to be more prevalent in children with FAS than their typically developing counterparts (Church, Eldis, Blakley, & Bawle, 1997; Church & Gerkin, 1988; Rössig, Wässer, & Oppermann, 1994). Conductive hearing loss related to recurrent otitis media has been commonly observed in children with craniofacial anomalies, including those with FAS, at rates ranging from 38% to 93% (reviewed in Church & Kaltenbach, 1997). Importantly, however, there is little research exploring sensorineural or conductive hearing loss in individuals who have FASDs but do not have the sentinel physical findings (i.e., facial dysmorphia and/or growth deficiency) of FAS. Cohen-Kerem, Bar-Oz, Nulman, Papaioannou, and Koren (2007) observed hearing loss and otitis media to be no more prevalent in those with diagnoses across the fetal alcohol spectrum than is found in the general population, but confirmatory data are lacking. This potential divergence in prevalence of hearing loss in FAS versus other FASDs may be due to an embryonic neuroectodermal syndrome hypothesized to underlie the craniofacial and ocular anomalies seen primarily in FAS; inner ear dysfunction may be associated with this syndrome (Church & Kaltenbach, 1997).

Research investigating the suprathreshold processing sequelae of prenatal alcohol exposure is even more limited and again has been restricted primarily to human subjects with FAS or laboratory animals exposed prenatally to moderate-to-heavy levels of alcohol. Slowed transmission of neural impulses in the auditory brainstem (Church, Abel, Kaltenbach, & Overbeck, 1996), delayed auditory event-related potentials (Kaneko, Riley, & Ehlers, 1993), and a reduction in the size of key auditory brainstem structures (Church & Kaltenbach, 1997) have been seen in prenatally exposed rats. Similarly, attenuated auditory event-related potentials have been observed in children with FAS (Kaneko, Ehlers, Phillips, & Riley, 1996; reviewed in Church & Kaltenbach, 1997). Data regarding the functional consequences of suprathreshold deficits due to prenatal alcohol exposure are particularly sparse. In one of the sole behavioral studies to date, Church et al. (1997) observed listening deficits in 100% of children with FAS (n = 12) tested on sound-in-noise dichotic listening tasks; however, most of these individuals had comorbid hearing loss, rendering it difficult to disentangle the relationship between functional impairment, hearing loss, and suprathreshold deficits. Moreover, as with hearing loss, little is known about the prevalence of listening difficulties (defined by D. R. Moore, 2018, as problems with hearing or listening despite normal audiometry) or the potential for suprathreshold processing deficits in individuals with FASDs but without FAS (cf. Stephen et al., 2012).

To date, there has been no systematic investigation of auditory dysfunction across the fetal alcohol spectrum. The limited data available suggest that individuals who have FASDs but not FAS may be less likely to experience hearing loss due to the absence of structural impairments associated with an embryologic neuroectodermal syndrome. We therefore predict that atypical auditory behaviors on the Short Sensory Profile (SSP; McIntosh, Miller, Shyu, & Dunn, 1999)—a norm-referenced caregiver report questionnaire used clinically to assess sensory processing dysfunction—will be present in children with FASDs and will be unrelated to hearing loss. It is not obvious, a priori, whether such listening difficulties—which presumably derive chiefly from suprathreshold deficits associated with particular CNS processes that may or may not be coupled to those measures

of CNS dysfunction used to inform FASD diagnoses—will vary according to diagnostic severity.

To investigate this hypothesis and to more generally explore the prevalence and nature of auditory dysfunction across FASDs, we leveraged existing information about auditory-related behaviors and reported hearing status, in addition to other diagnostic and neurobehavioral variables (including standardized measures of cognition/IQ, attention, and language function) present in a clinical database collected by the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network (FAS DPN). Information about peripheral hearing status was obtained from caregiver-provided records and reports submitted to the database. Data regarding auditory behaviors were gleaned from caregiver ratings of child auditory function on the SSP, which assesses multiple "domains" of sensory processing. In this study, we focused on the "auditory filtering" domain, which consists primarily of five items on which caregivers are asked to rate their child's behavior in situations that require either attending to or tuning out sound stimuli (see Jirikowic, Thorne, McLaughlin, Lee, & Astley, 2018, for full analysis and discussion of results in this sample population across all SSP domains). The SSP items were formulated based on neurobehavioral theories of sensory processing and integration (Dunn, 1997) and therefore lack reference to the highly specified auditory processing theories of auditory science. However, the auditory filtering items nonetheless serve to provide a standardized clinical measure of higher order listening behaviors, with a particular focus on attentional processes. The central role of attention in the behaviors probed by these items has been confirmed by principal component analyses showing that ratings on the auditory filtering items (plus one other item from an earlier long-version Sensory Profile) cluster together into a discrete "inattention/distractibility" factor (Dunn & Brown, 1997).

Despite prior reports that auditory filtering is consistently one of the SSP domains on which children with FASDs are most often rated as demonstrating a "definite difference" (> 2 *SD*s below the normative mean; Abele-Webster, Magill-Evans, & Pei, 2012; Carr, Agnihotri, & Keightley, 2010; Franklin, Deitz, Jirikowic, & Astley, 2008; Hansen & Jirikowic, 2013; Jirikowic, Olson, & Kartin, 2008), there has been little discussion of the potential impairments that may underlie atypical auditory behaviors in children with FASDs (Abele-Webster et al., 2012). This study thus sought to investigate auditory dysfunction in FASDs by exploring auditory behavioral outcomes and their relationship to neurobehavioral measures and reported hearing loss as a means to generate preliminary hypotheses about the underlying mechanisms involved. The study had three specific aims:

- Specific Aim 1: to quantify the prevalence of atypical auditory behaviors—as measured by auditory filtering domain scores on the SSP—across the spectrum of fetal alcohol disorders. We hypothesized that the proportion of children rated with a definite difference in auditory filtering scores would be high across the fetal alcohol spectrum.
- Specific Aim 2: to explore whether atypical auditory filtering domain scores for children with FASDs are related to (a) reported hearing loss and/or (b) measures of cognition/IQ, attention, and language function indicative of CNS impairment. Using neurodevelopmental CNS impairment as a proxy for potential suprathreshold processing deficits, we hypothesized that atypical auditory filtering scores in children with FASDs would be related more strongly to these deficits than to reported hearing loss.
- Specific Aim 3: to quantify the prevalence of hearing loss across the spectrum of fetal alcohol disorders. We hypothesized that children with FAS would have a higher prevalence of reported hearing loss than children with other FASDs.

Method

Participants

Selected data from children seen at FAS DPN clinics between 2000 and 2016 were retrospectively examined. At the time of their diagnostic evaluation, all patients evaluated at these clinics were invited to have their FASD clinical data entered into the FAS DPN research database for use in future research studies. Patient/caregiver consent was obtained in accordance with University of Washington Human Subjects Division oversight and approval.

All patients in the FAS DPN database were evaluated for FASDs using the 4-Digit Diagnostic Code (updated and coded according to criteria from the 2004 version; Astley, 2004), an interdisciplinary approach to diagnosis guided by empirically validated criteria (Astley, 2004, 2013). The four digits of the FASD 4-Digit Diagnostic Code reflect the magnitude of expression of the four key diagnostic features of FAS, in the following order: (a) growth deficiency, (b) FAS facial phenotype, (c) CNS structural/functional abnormalities, and (d) prenatal alcohol exposure. The magnitude of expression of each feature is case defined and ranked independently on a 4-point Likert scale, with 1 reflecting complete absence of the FAS feature and 4 reflecting a strong and classic presentation of the feature. Each Likert rank is specifically case defined. There are 102 four-digit codes that fall broadly under the umbrella of FASDs. These codes cluster into four clinically meaningful diagnostic subcategories (Astley, 2004): FAS, partial FAS (PFAS), static encephalopathy/alcohol exposed (SE/AE), and neurobehavioral disorder/alcohol exposed (ND/AE).

Data used in this study were from children in the FAS DPN research database who met the following inclusionary criteria: (a) between 3.00 and 10.99 years old at the time of diagnostic clinic visit, (b) diagnosed with FASDs (FAS, PFAS, SE/AE, or ND/AE), and (c) had SSP results available in the research database. Any subjects with missing data on more than one third of the items in any SSP domain were excluded.

Measures

The FAS DPN research database contains more than 2,000 fields of information on each patient evaluated for FASDs. The selected variables used in this analysis were measures related to auditory behavior (auditory filtering scores on the SSP), reported hearing status (hearing loss and history of otitis media), and measures of growth, facial morphology, and CNS structure and function used to derive each child's 4-Digit Diagnostic Code FASD diagnosis. These variables are described in more detail below.

Auditory Behaviors

SSP. The SSP (McIntosh et al., 1999), standardized for ages 3–11 years, is a 38-item caregiver-report questionnaire designed to identify atypical behavioral responses to sensation. A short-form version of the longer Sensory Profile (Dunn, 1999), the SSP encompasses seven domains of sensory processing—tactile sensitivity, taste/smell sensitivity, movement sensitivity, underresponsive/seeks sensation, auditory filtering, low energy/ weak, and visual/auditory sensitivity—with total scores in each domain norm-referenced, based on the performance of 1,037 children without known disabilities (Dunn & Brown, 1997). The SSP is considered to be a reliable and valid measurement tool, with high internal consistency for total score (Cronbach's $\alpha = .96$) and section scores (Cronbach's $\alpha = .82$–$.89$; Cronbach's α for the auditory filtering domain = .87).

Scores from the SSP's auditory filtering domain are the primary focus of this study. The auditory filtering domain comprises six items focused on either attending to or tuning out sound stimuli:

- Item 22: is distracted or has trouble functioning if there is a lot of noise around
- Item 23: appears to not hear what you say (e.g., does not "tune in" to what you say, appears to ignore you)
- Item 24: can't work with background noise (e.g., fan, refrigerator)
- Item 25: has trouble completing tasks when the radio is on
- Item 26: doesn't respond when name is called but you know the child's hearing is OK
- Item 27: has difficulty paying attention

Caregivers rate their child's frequency of atypical sensory behaviors on a Likert scale ranging from 1 (*always exhibits this behavior*) to 5 (*never exhibits this behavior*). Lower scores indicate more atypical behaviors. Total scores across items in each domain are compared to a normative sample in order to derive "cut scores" (Dunn, 1999) that categorize domain scores into classification category groups reflecting either "typical performance" for a domain score $\leq$ 1 *SD* below the normative mean (i.e., auditory filtering cut scores: 23–30), "probable difference" for a domain score > 1 but < 2 *SD*s below the normative mean (i.e., auditory filtering cut scores: 20–22), or "definite difference" for a domain score $\geq$ 2 *SD*s below the normative mean (i.e., auditory filtering cut scores: 6–19).

We conducted our primary analyses on auditory filtering domain total (summed total of scores on the six auditory filtering items) classification categories. We also examined score profiles across the six individual items. Of particular interest were Items 23 and 26, which are the only auditory filtering items explicitly involving auditory-related tasks (hearing what is said/tuning in and responding when name is called, respectively) and therefore most closely approximate measurable sound-in-noise listening behaviors. In contrast, the other auditory filtering items, particularly Items 24 and 25, appear to be more related to sound sensitivity/distractibility than to listening behaviors.

Hearing Status

Hearing loss and history of otitis media. Data on hearing status are obtained by the FAS DPN team based on a careful review of the records available for a given patient, as hearing function is typically not prospectively evaluated as part of the FAS DPN diagnostic assessment. These clinical records yield heterogenous information about hearing function (see Table 1), occasionally including thresholds measured during pure-tone audiograms but more typically consisting of formal reports (e.g., medical office hearing screens, school hearing screens, play-based audiometric procedures) indicating whether or not the individual had "passed" a hearing screen (sometimes at a given sound level[s], sometimes not)—in addition to newborn hearing screens based on auditory brainstem response and sometimes otoacoustic emission testing. Caregiver report on functional hearing levels and/or caregiver report regarding history of otitis media was also included. Due to the varying nature and quality of these data, they were used to assess only reported hearing loss and history of otitis media; reliable information related to presumed etiology of hearing loss was not available in this data set. Reported hearing loss was coded dichotomously, defined as audiometric thresholds > 25 dB HL in one or both ears at any frequency tested and/or formal report documenting hearing loss. Normal/functional hearing was defined as (a) audiometric thresholds of 25 dB HL or better across all frequencies tested and/or formal document with report of hearing screen at a given sound successfully passed or (b) caregiver report of no hearing concerns. Hearing data that were inconclusive or unclear—for example, report of failed infant hearing screen but no indication of any subsequent auditory assessment or audiometric thresholds > 25 dB HL but note of concurrent nasal congestion—were classified as missing in order to keep normal/functional hearing and hearing loss categories distinct and operationally valid. Caregiver report of history of otitis media/middle ear infection was also captured based on the number of reported cases: 0, 1, 2, or 3 or more.

FASD Diagnosis and Measures of Physical Dysmorphia and Alcohol Exposure

4-Digit Diagnostic Code FASD diagnosis (FAS, PFAS, SE/AE, and ND/AE). See full description above, along with Astley (2004) for additional details.

Table 1. Demographic and clinical profiles of the study sample.

Characteristic	*N* (valid %)
Gender	
Female	124 (38.2)
Male	201 (61.8)
Age at diagnosis (years)	
3–5.9	117 (36.0)
6–10.9	208 (64.0)
M (*SD*), range	6.9 (2.1), 3.0–10.9
Race/ethnicity	
Caucasian	157 (48.3)
African American	33 (10.2)
Native American/Canadian	23 (7.1)
Hispanic	14 (4.3)
Other (including mixed race)	98 (30.2)
FASD diagnosis	
FAS	13 (4.0)
PFAS	19 (5.5)
SE/AE	96 (29.5)
ND/AE	197 (60.6)
Type of auditory report	
Threshold info from audiogram	83 (25.5)
Formal report, no thresholds	167 (51.4)
Newborn screening	15 (4.6)
Caregiver report regarding hearing	53 (16.3)
Not reported	7 (2.5)
Short Sensory Profile respondent	
Parent unspecified	170 (52.3)
Foster parent	56 (17.2)
Adoptive parent	27 (8.3)
Legal guardian	15 (4.6)
Other family	47 (14.5)
Not reported	10 (3.1)

Note. Demographic and clinical profiles of the 325 children with fetal alcohol spectrum disorder (FASD) in the clinical study sample. FASD diagnoses were made by an interdisciplinary team using the 4-Digit Diagnostic Code (Astley, 2004), based on four clinically meaningful diagnostic subcategories: FAS = fetal alcohol syndrome; PFAS = partial FAS; SE/AE = static encephalopathy/alcohol exposed; and ND/AE = neurobehavioral disorder/alcohol exposed.

Growth deficiency. This measure ("growth rank": 1 = *none*, 2 = *mild*, 3 = *moderate*, and 4 = *severe*), which yields the first digit in the FASD 4-Digit Diagnostic Code, documents the magnitude of prenatal and/or postnatal growth deficiency (see Astley, 2004, for additional details).

FAS facial phenotype. This measure ("face rank": 1 = *none*, 2 = *mild*, 3 = *moderate*, and 4 = *severe*), which yields the second digit in the FASD 4-Digit Diagnostic Code, documents the magnitude of expression of the FAS facial phenotype, as defined by short palpebral fissure lengths, a smooth philtrum, and a thin upper lip (see Astley, 2004, for additional details).

Likelihood of structural/neurodevelopmental CNS abnormality. This measure ("CNS rank": 1 = *unlikely*, 2 = *possible*, 3 = *probable*, and 4 = *definite*) yields the third digit in the FASD 4-Digit Diagnostic Code. The first three levels (1 = *unlikely*, 2 = *possible*, and 3 = *probable*) document presumed likelihood of CNS structural abnormality as assessed by the interdisciplinary FAS DPN team on the basis of a variety of standardized assessments of function including executive function, memory, cognition, social/adaptive skills, academic achievement, language, motor, attention, and activity level. The fourth level (4 = *definite*) documents potential CNS abnormality of presumed prenatal origin on the basis of structural (e.g., microcephaly or observable brain abnormalities) and/or neurological (e.g., seizures or other hard neurological signs) evidence. To the degree possible, clinical assessment rules out traumatic brain injury or postnatal disease processes unrelated to prenatal alcohol exposure in assigning CNS rank (see Astley, 2004, for additional details).

Microcephaly. Microcephaly (0 = *no*, 1 = *yes*) is defined by the FASD 4-Digit Diagnostic Code as an occipital frontal circumference 2 or more *SD*s below the mean (≤ third percentile; see Astley, 2004, for additional details).

Prenatal alcohol exposure. This measure ("alcohol rank": 1 = *confirmed absence of exposure*; 2 = *unknown exposure*; 3 = *confirmed exposure, level unknown or moderate*; and 4 = *confirmed exposure, level high*), which yields the fourth digit in the FASD 4-Digit Diagnostic Code, documents the magnitude of alcohol exposure. Alcohol exposure is ranked according to the quantity, timing, frequency, and certainty of exposure during pregnancy and is based on best available records and/or direct report from the biological mother/witnesses to the exposure. A diagnosis under the umbrella of FASDs requires a confirmed prenatal alcohol exposure (Rank 3 or 4) with one exception: FAS. A diagnosis of FAS requires the Rank 4 FAS facial phenotype, which is so highly specific to (caused only by) prenatal alcohol exposure that presence of the Rank 4 FAS facial phenotype offsets the need for a confirmed history of alcohol exposure (see Astley, 2004, for additional details).

Measures of CNS Function

In the context of a careful medical review to document any potential postnatal sources of underlying CNS abnormality (e.g., traumatic brain injury, seizure disorder), the FAS DPN clinical assessment of CNS function includes a review of available neurodevelopmental assessments in the medical record, as well as documentation of current CNS function using common behavioral measures. For the current study, the following clinical measures available in the record were used to gauge the presence and severity of neurodevelopmental CNS impairment.

Attention-deficit/hyperactivity disorder diagnosis. This variable (0 = *no*, 1 = *yes*) documents whether the subject has a confirmed previous diagnosis of attention-deficit/hyperactivity disorder (ADHD) from a qualified provider or as a result of the FAS DPN clinical assessment.

Cognition/full-scale IQ and language function. The following domains of function were analyzed using a 3-point severity score: 1 = *within normal limits*, that is, performance no lower than 0.9 *SD* below the mean; 2 = *mildly to moderately impaired*, that is, performance 1.0–1.9 *SD*s below the mean on a standardized measure; and 3 = *severely impaired*, that is, performance 2 or more *SD*s below the mean on a standardized measure. The severity score was derived by the FAS DPN clinical team based on aggregate data in each respective domain, including standardized test

scores administered as part of the diagnostic clinic and/or scores available in the clinical records.

Cognitive data included standardized IQ scores from a variety of norm-referenced tests for intellectual and cognitive abilities, including the Wechsler Intelligence Scale for Children (Wechsler, 2003), the Stanford–Binet Intelligence Scales(Bain & Allin, 2005), and the Differential Ability Scales (Elliott, 2007). Normal cognition was defined as full-scale IQ (FSIQ) > 85, mildly impaired as 70 < FSIQ ≤ 85, and severely impaired as FSIQ ≤ 70.

Language function was quantified by a range of both standardized and structured clinical assessments, including but not limited to the various editions of the Clinical Evaluation of Language Fundamentals (Semel, Wiig, & Secord, 2013), the Preschool Language Scale (Zimmerman, Steiner, & Pond, 2002), and the Comprehensive Assessment of Spoken Language (Carrow-Woolfolk, 1999), and assessment of narrative production. Both direct testing and information from a detailed review of records were used to establish a clinical ranking based on the 3-point severity scale described above.

Analyses

All analyses were conducted using SPSS Version 19.0. Descriptive statistics (means, standard deviations, proportions) were used to profile the study population. Relationships between auditory filtering domain score categories (typical performance, probable difference, and definite difference) and selected clinical variables (Aims 1 and 2) were assessed using chi-squared (χ^2) tests when outcomes were assessed on nominal scales and Mantel–Haenszel linear-by-linear association chi-squared tests of trend (χ^2_{MH}) when outcomes were assessed on ordinal scales. Similarly, relationships between variables related to peripheral hearing status and selected clinical variables (Aim 3) were evaluated using chi-squared, linear-by-linear, and Fisher's exact tests, as appropriate. Results were considered significant at two-sided p values of < .05. The effect sizes of significant results were estimated using Cramer's V (ϕ_C) for chi-squared analyses, Spearman correlation coefficient (ρ) for linear-by-linear trend tests (Agresti, 2007), and phi coefficients (ϕ) for Fisher's exact results. Post hoc tests were performed for significant omnibus chi-squared statistics by estimating the p value of the adjusted residuals (i.e., the z scores). Because of the exploratory nature of the study, p values for post hoc analyses should be interpreted with caution.

Results

The data set analyzed (N = 325) consisted of 124 girls and 201 boys, ranging in age from 3.03 to 10.97 years. Table 1 provides demographic and clinical characteristics and data type/origin. In this sample, the largest proportion of children were diagnosed with ND/AE, followed by SE/AE. As expected, about one of 10 children was diagnosed with FAS or PFAS. This study sample is a good representation of the larger FAS DPN population (see Astley, 2010; see Table 2).

Of the 325 participants who met the inclusionary criteria (which included data available for at least two thirds of the SSP items in any given domain), 43 individuals were still missing some SSP data, nine of whom were missing data in the auditory filtering domain. To handle these missing data, the average of the subjects' remaining scores in the incomplete domain was calculated, and this value replaced the missing score(s) in that domain, for that subject. This approach was selected to control for bias while still fairly representing the child's auditory filtering profile. To maintain the ordinal format of the data, those newly calculated item scores that were not whole numbers were rounded to the closest whole number.

Aim 1: Prevalence of Atypical Auditory Behaviors Across FASD Diagnoses

A majority (80.0%) of children with FASDs in our clinical sample were rated by their caregivers as exhibiting a definite difference (2 *SD*s below the normative mean) on the auditory filtering domain of the SSP (see Figure 1). No significant linear relationship was observed between outcomes on auditory filtering domain score categories and severity of FASD diagnosis; however, the raw cross-tabulation numbers unexpectedly show that the percentage of children diagnosed with FAS who were reported with a definite difference on the auditory filtering items (61.5%) was lower than the equivalent figure for children with either PFAS (78.9%), SD/AE (87.5%), or ND/AE (77.7%). Correspondingly, the percentage of children with FAS rated with typical performance was higher than those with less severe diagnoses (see Table 2, top). When the cross-tabulation was collapsed to assess the prevalence of definite difference reported among FAS (61.5%) versus all other FASD diagnoses combined (80.8%), the contrast remained nonsignificant (Fisher's exact test, p = .19).

Due to this unexpected (albeit nonsignificant) finding in which children with less severe FASD diagnoses were more frequently rated with atypical auditory behaviors than were children with FAS, post hoc analyses were conducted to more closely examine the relationships between auditory filtering outcomes and various physical features of FASDs (i.e., growth deficiency, FAS facial features, likelihood of CNS structural abnormalities and microcephaly), in addition to prenatal alcohol exposure (see Table 2, bottom). The post hoc analyses revealed a similar pattern of association. Atypical auditory behaviors were prevalent across the full spectrum of physical outcomes and tended to be more prevalent among those with less severe physical outcomes, especially those with less severe facial features.

Aim 2: Relationship Between Atypical Auditory Behaviors and Measures Indicative of Reported Hearing Dysfunction or CNS Impairment

No observable relationship was found between outcomes on auditory filtering domain score categories and measures of peripheral hearing status, either reported hearing loss or

Table 2. Prevalence of Short Sensory Profile auditory filtering domain scores across fetal alcohol spectrum disorder (FASD) diagnoses.

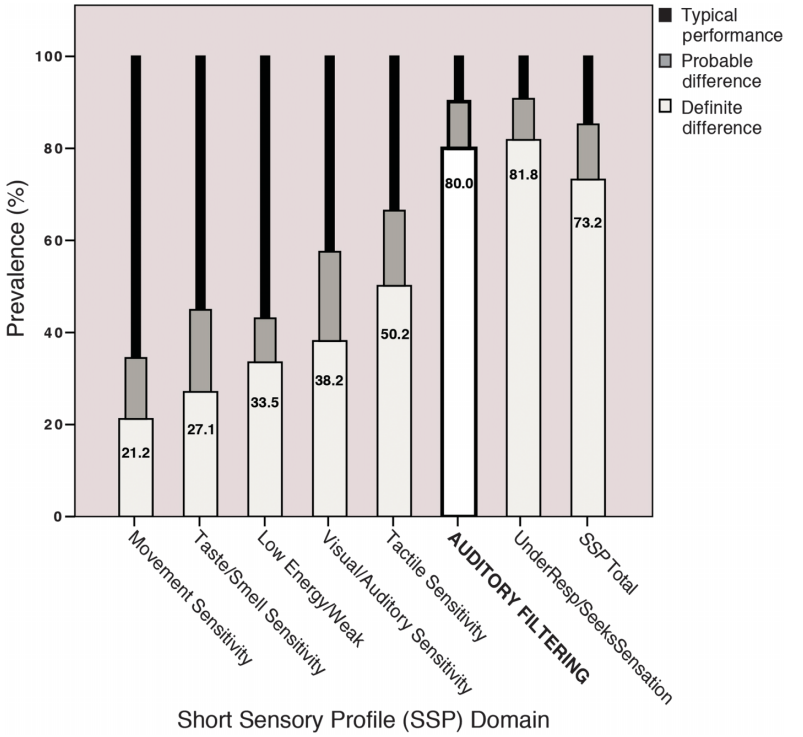
	Auditory filtering domain score category			
	Definite difference	Probable difference	Typical performance	
FASD diagnostic features	***n*** **(valid %)**	***n*** **(valid %)**	***n*** **(valid %)**	**Statistic (*p*) [effect size]**
Prevalence				
Overall	260 (80.0)	33 (10.2)	32 (9.8)	—
By FASD diagnosis				Linear $\chi^2_{MH}(1, N = 325) = 0.02$ (.88)
ND/AE	153 (77.7)	21 (10.7)	23 (11.7)	
SE/AE	84 (87.5)	8 (8.3)	4 (4.2)	
PFAS	15 (78.9)	3 (15.8)	1 (5.3)	
FAS	8 (61.5)	1 (7.7)	4 (30.8)	
Post hoc analyses: association between SSP auditory filtering domain score categories and physical features of FASD and prenatal alcohol exposure				
Growth deficiency (growth rank)				Linear $\chi^2_{MH}(1, N = 325) = 1.59$ (.21)
1: Normal	199 (80.6)	26 (10.5)	22 (8.9)	
2: Mild	31 (83.8)	2 (5.4)	4 (10.8)	
3: Moderate	16 (76.2)	3 (14.3)	2 (9.5)	
4: Severe	14 (70.0)	2 (10.0)	4 (20.0)	
FAS facial phenotype (face rank)				Linear $\chi^2_{MH}(1, N = 325) =$ **18.48 (<. 001) [ρ = –.24]**
1: Normal	147 (89.1)	11 (6.7)	7 (4.2)	
2: Mild	82 (72.6)	16 (14.2)	15 (13.3)	
3: Moderate	21 (67.7)	4 (12.9.7)	6 (19.4)	
4: Severe	10 (62.5)	2 (12.5)	4 (25.0)	
Likelihood of CNS structural abnormality (CNS rank)				Linear $\chi^2_{MH}(1, N = 325) = 0.52$ (.47)
1: Unlikely	0 (0.0)	0 (0.0)	0 (0.0)	
2: Possible	153 (77.7)	21 (10.7)	23 (11.7)	
3: Probable	65 (87.8)	6 (8.1)	3 (4.1)	
4: Definite	42 (77.8)	6 (11.1)	6 (11.1)	
Microcephaly				Linear $\chi^2_{MH}(1, N = 321) = 2.24$ (.13)
No	227 (81.1)	28 (10.0)	25 (8.9)	
Yes (< 3 percentile)	30 (73.2)	4 (9.8)	7 (17.1)	
Prenatal alcohol exposure (alcohol rank)				Linear $\chi^2_{MH}(1, N = 323) = 2.47$ (.12)
3: Moderate	124 (77.5)	16 (10.0)	20 (12.5)	
4: High	135 (82.8)	17 (10.4)	11 (6.7)	

Note. Prevalence of Short Sensory Profile auditory filtering domain scores across FASD diagnoses. No linear relationship between auditory filtering scores ("definite difference": domain score ≥ 2 *SD*s below the normative mean; "probable difference": domain score > 1 but < 2 *SD*s below the normative mean; or "typical performance": domain score ≤ 1 *SD* below the normative mean) and FASD diagnosis was observed (FASD diagnostic abbreviations [Astley, 2004]: fetal alcohol syndrome [FAS], partial FAS [PFAS], static encephalopathy/alcohol exposed [SE/AE], and neurobehavioral disorder/alcohol exposed [ND/AE]). Post hoc analyses of the relationship between auditory filtering scores and physical features of FASD show that atypical auditory behaviors tended to be more prevalent among those with less severe physical outcomes, especially less severe facial features. The four key diagnostic features of FASD (growth deficiency, FAS facial phenotype, CNS abnormalities, and prenatal alcohol exposure) are case defined on 4-point Likert scales (ranks) and comprise the four digits of the FASD 4-Digit Diagnostic Code (Astley, 2004). Alcohol Ranks 1 and 2 are not included here because individuals diagnosed with FASD cannot by definition have Alcohol Rank 1 (confirmed lack of prenatal alcohol exposure) and Alcohol Rank 2 (unknown, indicates unknown prenatal alcohol exposure). SSP = Short Sensory Profile; CNS = central nervous system. Bold values are significant at $p < .05$.

history of otitis media (see Table 3, top). With respect to measures associated with CNS impairment (see Table 3, bottom), there was no observable relationship between auditory filtering outcomes and FSIQ scores or language function; however, a relationship between auditory filtering scores and ADHD diagnosis was observed. Post hoc analyses documented a high prevalence of children with a definite difference in auditory filtering scores among those with (88.3%) and without (72.6%) ADHD, but the prevalence was significantly higher among those with ADHD.

We additionally assessed the effect of age on auditory filtering outcomes in order to ensure that none of the observed relationships was confounded by age. Based on data reported by Dunn (1999) indicating that younger and older children may score differently on some sections of the long-form Sensory Profile (with scores indicating that younger children may perform better on items related to inattention/distractibility), we split the sample into two groups. They were (a) preschool children (3.00–5.99 years old at the time of FAS DPN clinic visit) and (b) school-aged children (6.00–10.99 years old at clinic visit). This split was also motivated by the knowledge that school-aged children may have a wider range of cognitive assessments available in the clinical record to examine the relationships between auditory behaviors and CNS function. A chi-squared test comparing outcomes on auditory filtering domain score categories across groups did show an effect of age, $\chi^2(2, N = 325) = 9.40$, $p = .009$, $\phi_C = .17$, with post hoc comparisons indicating that definite differences in auditory filtering were more likely to be reported ($p = .005$) in the older age group

Figure 1. Profile of Short Sensory Profile domain scores in the clinical study sample of 325 children diagnosed with fetal alcohol spectrum disorders. Represented here is the percentage of children whose total score in each domain (and total score across all domains: "SSP Total") falls into the categories of "definite difference" (light gray bars, except in the case of the auditory filtering domain, which is white for emphasis): domain score ≥ 2 *SD*s below the normative mean; "probable difference" (dark gray bars): domain score > 1 but < 2 *SD*s below the normative mean; or "typical performance" (black bars): domain score ≤ 1 *SD* below the normative mean. Auditory filtering domain scores showed among the highest ratings of children with definite and probable differences.



(85.1% with a definite difference among children 6 years of age and older) than in the younger (70.9% with a definite difference among those less than 6 years of age), consistent with Dunn's findings. Based on this information, we separately assessed the influence of age on the relationship between auditory filtering outcomes and each of the diagnostic, neurobehavioral, and hearing-related variables probed in the study. We found that the presence (or lack thereof) of a linear relationship to auditory filtering outcomes did not differ between the two age groups for any of the variables examined with the exception of language function, where a linear relationship between auditory filtering scores and language function was observed in the older group, $\chi^2_{MH}(1, N = 199) = 6.11$, $p = .013$, but not the younger, $\chi^2_{MH}(1, N = 110) = 1.67$, $p = .194$. The prevalence of older children with a definite difference in auditory filtering scores was highest among those rated as having "severely impaired" language function (92.0%). This is approximately 10 percentage points higher than among those with "mildly to moderately impaired" language function (82.9%) and those without language impairment (79.6%).

Aim 3: Assessing the Relationship Between Hearing Status and FASD Diagnostic Measures

Relationships between measures of peripheral hearing status and FASD diagnosis—including component assessments of the presence of the physical features of FASDs (FAS facial phenotype, growth deficiency, likelihood of CNS structural abnormality, and microcephaly), magnitude of prenatal alcohol exposure, and FSIQ—were assessed (see Table 4). Reported hearing loss (defined as reported audiometric thresholds > 25 dB HL in one or both ears at any frequency tested or formal report documenting hearing loss) was 16-fold more prevalent among the children diagnosed with FAS (40%: four individuals with reported hearing loss out of the 10 individuals with FAS with sufficient hearing/audiometric information in the data set) than among the children diagnosed with other FASD diagnoses (2.4%: seven with reported hearing loss out of 286 individuals [PFAS = 17, SE/AE = 88, ND/AE = 181]; see Figure 2, left). The prevalence of hearing loss increased linearly with increasing severity of FASD diagnosis. In contrast, no significant

Table 3. Short Sensory Profile auditory filtering domain scores: association with reported hearing status and central nervous system (CNS) function.

	Auditory filtering domain categories			
	Definite difference	Probable difference	Typical performance	
Hearing and CNS status	***n* (valid %)**	***n* (valid %)**	***n* (valid %)**	**Statistic (*p*) [effect size]**
Reported hearing loss (HL)				Linear $\chi^2_{MH}(1, N = 296) = 0.24$ (.62)
Normal/functional	233 (81.8)	27 (9.5)	25 (8.8)	
HL (one or both ears)	9 (81.8)	0 (0.0)	2 (18.2)	
Reported otitis media				Linear $\chi^2_{MH}(1, N = 319) = 1.89$ (.17)
No cases reported	132 (77.6)	16 (9.4)	22 (12.9)	
1–2 cases reported	36 (85.7)	4 (9.5)	2 (4.8)	
3+ cases reported	87 (81.3)	13 (12.1)	7 (6.5)	
Full-scale IQ (standard score)				Linear $\chi^2_{MH}(1, N = 287) = 2.11$ (.15)
Normal: > 85	98 (78.4)	11 (8.8)	16 (12.8)	
Mildly impaired: > 70 and ≤ 85	93 (80.2)	15 (12.9)	8 (6.9)	
Severely impaired: ≤ 70	40 (87.0)	3 (6.5)	3 (6.5)	
ADHD diagnosis				Linear $\chi^2_{MH}(1, N = 309) =$ **15.79 (< .001) [ρ = .21]**
No	119 (72.6)	19 (11.6)	26 (15.9)	
Yes	128 (88.3)	13 (9.0)	4 (2.8)	
Language function				Linear $\chi^2_{MH}(1, N = 309) = 1.04$ (.31)
Normal	76 (77.6)	9 (9.2)	13 (13.3)	
Mildly impaired	82 (83.7)	9 (9.2)	7 (7.1)	
Severely impaired	92 (81.4)	12 (10.6)	9 (8.0)	

Note. Association between Short Sensory Profile auditory filtering domain scores ("definite difference": domain score ≥ 2 *SD*s below the normative mean; "probable difference": domain score > 1 but < 2 *SD*s below the normative mean; or "typical performance": domain score ≤ 1 *SD* below the normative mean) and reported hearing status and CNS function. Hearing loss defined as thresholds > 25 dB HL at any frequency tested and/or formal report documenting hearing loss. Whereas atypical auditory behaviors were more prevalent among children with attention-deficit/hyperactivity disorder (ADHD), no linear relationships between auditory filtering scores and measures of hearing status were observed. See text for operational definitions of the three language function categories. Bold values are significant at $p < .05$.2

relationship between history of otitis media and FASD diagnosis was observed (see Table 4 and Figure 2 [right]).

The prevalence of reported hearing loss increased significantly and linearly with increasing severity of growth deficiency, FAS facial phenotype, likelihood of CNS structural abnormality, and FSIQ deficit. Reported hearing loss was also significantly more prevalent among children with microcephaly. Although the prevalence of reported hearing loss among the children with high alcohol exposure was twofold greater than among children with moderate exposures, this contrast was not statistically significant. With respect to reported history of otitis media, no significant associations were observed with any of the FASD diagnostic variables examined.

Discussion

The present results were obtained from a retrospective examination of data collected from children who were diagnosed with FASDs at Washington State FAS DPN clinics. They indicate that a large proportion of children with FASDs exhibit atypical, higher order auditory behaviors involving attending to or tuning out sound stimuli, as measured by caregiver ratings on the auditory filtering domain of the SSP. The prevalence of atypical auditory behaviors in this population was not observed to be significantly related to severity of FASD diagnosis; that is, a comparably high proportion of children were reported with a definite difference in auditory filtering across fetal alcohol diagnoses. No relationship was observed between atypical auditory behaviors and reported estimates of peripheral hearing function—including hearing loss and history of otitis media potentially indicative of conductive hearing issues—based on data obtained from caregiver-provided records and reports. There was a relationship, however, between atypical auditory behaviors and ADHD diagnosis, presumably reflective of underlying CNS impairment. Children with ADHD were more likely to be reported with atypical behaviors in the auditory filtering domain. The prevalence of atypical auditory behaviors was not observed to be correlated across the sample with other measures of CNS function, including measures of cognition and language function.

Reported hearing loss was found to be related to FASD diagnosis; that is, hearing loss was 16-fold more prevalent among children with FAS (40%) than among children with other FASDs (2.4%), for whom the prevalence of hearing loss was similar to that estimated for the general U.S. adolescent population (2.3%; Lin, Niparko, & Ferrucci, 2011). An increased prevalence of reported hearing loss was also correlated with the presence of physical features associated with FAS: growth deficiency, facial dysmorphia, likelihood of CNS damage, and microcephaly. Reported hearing loss was also related to lower FSIQ scores but was not observed to be significantly related to the reported

Table 4. Association between reported hearing loss, otitis media, fetal alcohol spectrum disorder (FASD) diagnosis, and FASD features.

FASD diagnostic features	Reported hearing loss (one or two ears)		Reported cases: otitis media (OM)	
	Hearing loss, *n* (valid %)	Statistic (*p*) [effect size]	OM: 3+ cases, *n* (valid %)	Statistic (*p*) [effect size]
FASD diagnosis	Linear $\chi^2_{MH}(1, N = 296)$ = **17.77 (< .001) [ρ = –.15]**		Linear $\chi^2_{MH}(1, N = 319)$ = 0.23 (.63)	
ND/AE	4 (2.2)		71 (36.4)	
SE/AE	2 (2.3)		27 (29.0)	
PFAS	1 (5.9)		4 (21.1)	
FAS	4 (40.0)		5 (41.7)	
Growth deficiency (growth rank)	Linear $\chi^2_{MH}(1, N = 296)$ = **7.32 (.007) [ρ = .15]**		Linear $\chi^2_{MH}(1, N = 319)$ = 1.15 (.28)	
1: Normal	5 (2.2)		83 (34.3)	
2: Mild	3 (8.3)		13 (37.1)	
3: Moderate	0 (0.0)		6 (28.6)	
4: Severe	3 (17.6)		5 (23.8)	
FAS facial phenotype (face rank)	Linear $\chi^2_{MH}(1, N = 296)$ = **16.74 (< .001) [ρ = .17]**		Linear $\chi^2_{MH}(1, N = 319)$ = 0.52 (.47)	
1: Normal	3 (1.9)		59 (36.6)	
2: Mild	2 (2.0)		33 (29.5)	
3: Moderate	2 (7.7)		9 (29.0)	
4: Severe	4 (30.8)		6 (40.0)	
Likelihood of CNS structural abnormality (CNS rank)	Linear $\chi^2_{MH}(1, N = 296)$ = **4.47 (.04) [ρ = .12]**		Linear $\chi^2_{MH}(1, N = 319)$ = 0.45 (.50)	
1: Unlikely	0 (0.0)		0 (0.0)	
2: Possible	4 (2.2)		71 (36.4)	
3: Probable	3 (4.2)		20 (27.8)	
4: Definite	4 (9.1)		16 (30.8)	
Microcephaly	Fisher's exact (*N* = 292) **(.02) [φ = .15]**		Linear $\chi^2_{MH}(1, N = 314)$ = 0.94 (.33)	
No	7 (2.7)		95 (34.5)	
Yes (≤ 3rd percentile)	4 (11.8)		10 (25.6)	
Prenatal alcohol exposure (alcohol rank)	Fisher's exact (*N* = 294) (.22)		Linear $\chi^2_{MH}(1, N = 317)$ = 0.81 (.37)	
3: Moderate	3 (2.0)		47 (29.9)	
4: High	8 (5.4)		59 (36.9)	
Full-scale IQ (standard score)	Linear $\chi^2_{MH}(1, N = 259)$ = **4.00 (.045) [ρ = .12]**		Linear $\chi^2_{MH}(1, N = 282)$ = 3.71 (.05)	
Normal (> 85)	1 (0.9)		48 (39.0)	
Mildly impaired (> 70 and ≤ 85)	4 (3.8)		35 (30.7)	
Severely impaired: (≤ 70)	3 (6.8)		11 (24.4)	

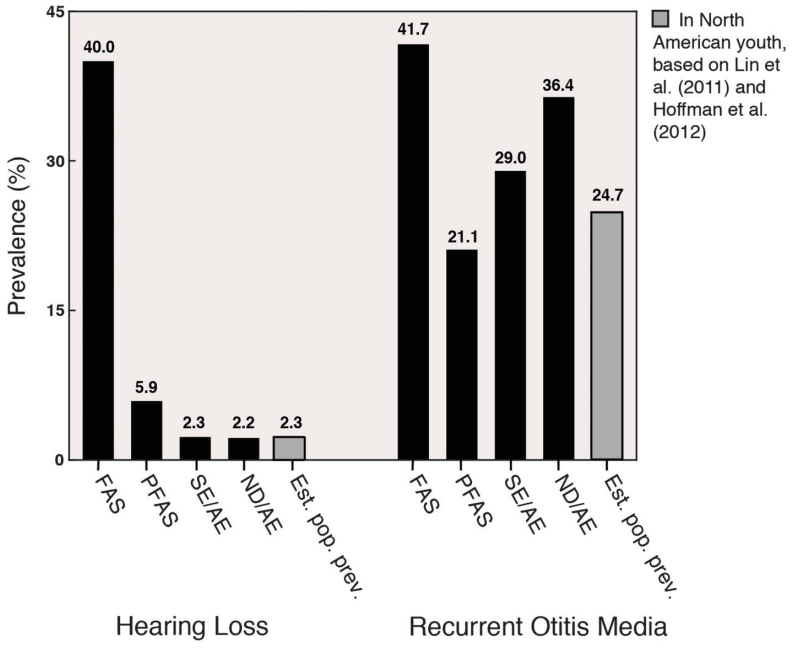
Note. Association between hearing status (reported hearing loss and otitis media) and FASD diagnosis (abbreviations: ND/AE = neurobehavioral disorder/alcohol exposed; SE/AE = static encephalopathy/alcohol exposed; PFAS = partial FAS; and FAS = fetal alcohol syndrome [Astley, 2004]) and diagnostic physical features of FASDs. Reported hearing loss (see text for operational definition) was more prevalent among children diagnosed with FAS than with other FASD diagnoses, whereas no significant relationship between history of otitis media and FASD diagnosis was observed. (Values for *n* and valid % are shown here only for 3+ cases of otitis media, but analyses related to otitis media are conducted across three categories: 0 cases, 1–2 documented cases, and 3+ cases.) The prevalence of reported hearing loss increased with increasing severity of growth deficiency, FAS facial phenotype, likelihood of central nervous system (CNS) structural abnormality, microcephaly, and full-scale IQ deficit. No such relationships were observed with respect to reported history of otitis media; no significant associations were observed with any of the FASD diagnostic variables examined. The four key diagnostic features of FASD (growth deficiency, FAS facial phenotype, CNS abnormalities, and prenatal alcohol exposure) are case defined on 4-point Likert scales (ranks) and comprise the four digits of the FASD 4-Digit Diagnostic Code (Astley, 2004). Alcohol Ranks 1 and 2 are not included here because individuals diagnosed with FASD cannot by definition have Alcohol Rank 1 (confirmed lack of prenatal alcohol exposure) and Alcohol Rank 2 (unknown, indicates unknown prenatal alcohol exposure). Bold values are significant at $p < .05$.

magnitude of prenatal alcohol exposure. In contrast, reported history of otitis media did not differ according to any of the above measures, including FASD diagnosis or the physical features of FAS. It is important to note that reported hearing loss was based on retrospective record review, not prospective audiologic assessment. Moreover, a relatively small number of individuals in the study sample were reported with hearing loss. Based on these two limitations, the present findings related to hearing loss should be interpreted with caution.

Auditory Dysfunction in Children With FASDs

The observed prominence of auditory filtering as one of the SSP domains in which caregivers rated their children with the highest frequencies of problem behaviors is consistent with previous findings in children diagnosed with FASDs (Abele-Webster et al., 2012; Carr et al., 2010; Franklin et al., 2008; Hansen & Jirikowic, 2013). Although there is evidence to suggest that one of the teratogenic effects of alcohol is insult to the developing auditory periphery that may impact audiometric hearing thresholds (Church & Kaltenbach, 1997), less is known about damage to other mechanisms—potentially centrally mediated—that may be implicated in the sound-in-noise listening and sound sensitivity/distractibility behaviors probed by the SSP. The present finding that the prevalence of atypical auditory behavior reported on the SSP is comparably high across the fetal alcohol spectrum is consistent with data from Carr et al. (2010) showing that 88% of children

Figure 2. Reported hearing loss (see text for operational definition) and recurrent otitis media (3+ occurrences) across fetal alcohol spectrum disorder (FASD) diagnoses (FASD diagnostic abbreviations [Astley, 2004]: fetal alcohol syndrome [FAS], partial FAS [PFAS], static encephalopathy/alcohol exposed [SE/AE], and neurobehavioral disorder/alcohol exposed [ND/AE]) and diagnostic/physical features of FASDs. Reported hearing loss was 16-fold more prevalent among children diagnosed with FAS (four out of 10 individuals with FAS were reported with hearing loss) than with other FASD diagnoses (seven out of 286 individuals reported with hearing loss; a prevalence similar to that observed in the general U.S. adolescent population [Lin et al., 2011]). History of recurrent otitis media was not observed to vary significantly across FASD diagnoses.



with alcohol-related neurodevelopmental disorder (analogous to ND/AE and SE/AE) and 80% of those with PFAS were rated with definite auditory filtering differences. Together, these findings suggest that these atypical auditory behaviors are widespread in individuals with FASDs, even those without the observable physical markers of FAS or PFAS. Although the prevalence of FAS itself is estimated to be one to three per 1,000 live births in the general population (Stratton, Howe, & Battaglia, 1996), individuals with fetal alcohol-related disorders across the entire spectrum are far more numerous (see Astley, 2010; Sampson et al., 1997), underscoring the clinically driven imperative to better characterize and understand auditory dysfunction across FASDs.

It is notable, however, that the atypical auditory behaviors seen on the SSP are not specific to FASDs. Whereas low auditory filtering scores do not appear to be common in typically developing children (for whom Tomchek and Dunn [2007] observed the lowest ratings of definite differences [3.1%] across domains to be in auditory filtering), children with a variety of neurodevelopmental disorders are frequently rated with atypical auditory filtering scores. In particular, 78% of toddlers (Tomchek & Dunn, 2007) and 70% of older children (Green, Chandler, Charman, Simonoff, & Baird, 2016) with autism spectrum disorder (ASD) were rated with a definite difference in the auditory filtering domain (see also Al-Heizan, AlAbdulwahab, & Kachanathu, 2015; Ashburner, Ziviani, & Rodger, 2008; Baker, Lane, Angley, & Young, 2008; Chen, Rodgers, & McConachie, 2009; O'Donnell, Deitz, Kartin, Nalty, & Dawson, 2012; Tomchek, Huebner, & Dunn, 2014). For children with Down syndrome (Bruni, Cameron, Dua, & Noy, 2010), Williams syndrome (John & Mervis, 2010), and moderate intellectual developmental disabilities (Engel-Yeger, Hardal-Nasser, & Gal, 2011), SSP profiles in which definite differences in auditory filtering scores deviate from typical (43%, 59%, and 50%, respectively), but not notably more so than other domains, have also been observed.

Hearing Loss Versus Listening Difficulties in Children With FASDs

The lack of any observed relationship between low auditory filtering scores in children with FASDs and reported hearing status (either hearing loss or general conductive hearing concerns as represented by episodes of otitis media) preliminarily suggests that audibility was not a factor in the atypical auditory behaviors reported on the SSP. The finding that audibility issues (i.e., reported hearing loss) were no more prevalent in children diagnosed with an FASD

other than FAS compared to the general U.S. adolescent population (Lin et al., 2011), but were elevated in children with FAS, is consistent with previous data (Church & Gerkin, 1988; Church et al., 1997; Cohen-Kerem et al., 2007; Rössig et al., 1994). Church and Kaltenbach (1997) hypothesized that there may be a relationship between the craniofacial abnormalities seen in FAS and inner ear dysfunction, based on shared embryological origins in ectodermal tissue potentially susceptible to damage from prenatal alcohol exposure. The present finding that reported hearing loss is related to the severity of facial dysmorphia supports this hypothesis. However, hearing loss was additionally related to all of the other physical markers of FAS—including growth deficiency, likelihood of CNS structural abnormality, and microcephaly—which may or may not be associated with neuroectodermal impairments. It is possible that the gross structural sequelae of prenatal alcohol exposure—including structural deficits involving the inner ear—are somehow related. Notably, no significant relationship was seen between hearing loss and magnitude of prenatal alcohol exposure, although the lack of relationship observed may be due to potential unreliability of the data.

In contrast, reported episodes of otitis media typically associated with middle ear function were not observed to vary across FASD diagnoses. Rates of recurrent otitis media did not appear to differ greatly than would be expected in typically developing American children (Hoffman et al., 2013), contrary to past observations of increased otitis media in FAS (Church et al., 1997; Rössig et al., 1994). This difference may be due to the widespread adoption of the pneumococcal conjugate vaccine beginning in the early 2000s (Qureishi, Lee, Belfield, Birchall, & Daniel, 2014), which is reported to have precipitated a 28% drop in the annual prevalence of otitis media diagnoses in the United States between 1997 and 2007 (Hoffman et al., 2013).

Due to the reliance on retrospective record review rather than direct audiologic assessment at the time of the FAS DPN clinic visit, the above findings are preliminary. However, they do suggest that audibility is not a factor in the atypical auditory behaviors reported in children with FASDs. These listening difficulties—namely, problems with hearing or listening despite normal audiometry—are prevalent across FASDs. Listening difficulties, which have been linked to the controversial clinical diagnosis of (central) auditory processing disorder ([C]APD; American Academy of Audiology, 2010; American Speech-Language-Hearing Association, 2005), are frequently reported in children with a variety of developmental disorders, including specific language impairment, dyslexia, and ADHD (reviewed in de Wit et al., 2018), in addition to children without any known neurodevelopmental disorders. Depending on the diagnostic criteria they used, Wilson and Arnott (2013) found that anywhere from 7% to 96% of a sample of typically developing children could be said to have listening difficulties potentially indicative of CAPD.

There is a vast array of distinct but interrelated, centrally mediated suprathreshold auditory processes that support sound-in-noise listening, including accurate lower order encoding of temporal and spatial attributes of the sound signal (reviewed in Bharadwaj et al., 2015; Stecker & Gallun, 2012) and intact spatial hearing processes (Cameron, Dillon, Glyde, Kanthan, & Kania, 2014). Each of these processes is critical to higher order operations by which the brain segregates the multitude of sound signals arriving at the ear into meaningful "auditory objects" (Griffiths & Warren, 2004; Shinn-Cunningham, 2008). Moreover, as detailed by D. R. Moore (2018), complex listening tasks such as those probed by some of the SSP auditory filtering items and other more auditory-specific tests depend not only on this interrelated network of central auditory processes but also on mechanisms more traditionally associated with the auditory periphery (e.g., high-threshold auditory nerve fiber synapses; see Kujawa & Liberman, 2015) and on central processes typically considered cognitive (e.g., attention, memory, and emotion). These cognitive processes interact with but may or may not involve auditory-specific components. Attention and other cognitive control processes are necessary to focus cognitive resources on the sound target (Anderson & Kraus, 2010; Eckert, Teubner-Rhodes, & Vaden, 2016; Fritz, Elhilali, David, & Shamma, 2007). In addition, they facilitate the quick switching of attention between spatiotemporal acoustic cues in order to enhance focus on relevant sound sources/speakers (an operation termed *active listening*, which is essential to following conversations in noisy, multitalker settings: see Larson & Lee, 2013, 2014; Shinn-Cunningham et al., 2017). All of these suprathreshold mechanisms are susceptible to breakdown and may be implicated in the listening difficulties observed in children with FASDs.

Although it is beyond the scope of this study to investigate the mechanisms of impairment underlying listening difficulties in children with FASDs, the preliminary finding that ADHD was related to atypical auditory filtering scores suggests that attention may play an important role in such auditory dysfunction. A relationship between the features of ADHD and presumed (C)APD has been previously reported (reviewed in de Wit et al., 2018), leading to a suggestion that (C)APD may, in some cases, simply reflect amodal attentional deficits (absent any auditory-specific processes) already captured by ADHD diagnosis. Of three studies reviewed by de Wit et al. that compare performance on various standardized assessments between children diagnosed with presumed (C)APD and those with ADHD, one observed auditory and visual duration pattern test performance differences between groups (Bellis, Billiet, & Ross, 2011). Although it is not possible based on the present results to ascertain whether auditory-specific or more general attentional deficits are related to listening difficulties in FASDs, previous evidence suggests that auditory filtering ratings do capture a construct distinct from ADHD. In a study of 46 children with FASDs, Carr et al. (2010) found that some auditory filtering scores differed according to FASD diagnosis, yet only one participant had ADHD, although all had received formal assessment. Moreover, Abele-Webster et al. (2012) found no correlation between the attention-deficit/hyperactivity index of the Conners' Parent Rating

Scales and any SSP domain scores and concluded that sensory processing problems in children with FASDs are distinct from ADHD. Although rates of comorbid ADHD and FASDs are typically high—53.9% of the larger FAS DPN population was diagnosed with ADHD (Astley, 2010, Table 11), and other researchers have estimated that up to 95% of children with FASDs have ADHD (Fryer, McGee, Matt, Riley, & Mattson, 2007)—Kodali et al. (2017) report that patterns of brain activity related to executive function differ between the two disorders. A meta-analysis by Kingdon, Cardoso, and McGrath (2016) also showed distinct patterns of executive function behavior deficits, with more extensive set-shifting impairments in FASDs. Such set-shifting impairments may be associated with attentional switching deficits that could negatively impact active listening behaviors.

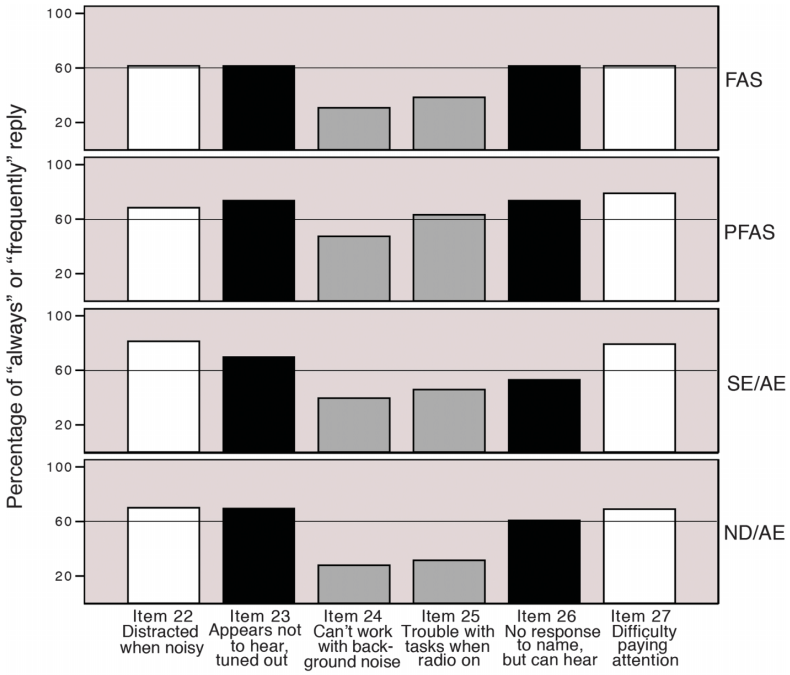
To get a better sense of the specific behaviors driving the low auditory filtering scores observed in this study, we explored the overall caregiver-response profile across individual auditory filtering items (22–27; see Figure 3). Although not formulated to specifically probe sound-in-noise listening, some of the SSP items at least partially capture these behaviors. Items 23 ("appears to not hear what you say [for example, does not 'tune in' to what you say, appears to ignore you]") and 26 ("doesn't respond when name is called but you know the child's hearing is OK") do explicitly assess listening behaviors, and although there is no mention of the acoustic environment, it is reasonable to assume that noise may play a role in the scenarios caregivers envision when rating their child's behavior. In contrast, Items 24 ("can't work with background noise [for example, fan, refrigerator]") and 25 ("has trouble completing tasks when the radio is on") appear to interrogate behaviors related to sound sensitivity or distractibility. As can be seen in Figure 3, the percentage of caregivers responding that their child "always or 'frequently" exhibits the described negative behavior was higher for Items 23 and 26 (black bars) than for Items 24 and 25 (gray bars), across FASD diagnoses. This suggests that problematic listening behaviors more strongly impacted the low auditory filtering ratings observed than did sound sensitivity/distractibility. Interestingly, Tomchek and Dunn (2007) reported similar results in children with ASD, with 73% and 51% responding "always/frequently" to Items 23 and 26, respectively, versus 13% and 16% to Items 24 and 25. Other auditory filtering items that consistently received atypical ratings for the children with FASDs in the study sample were Items 27 ("has difficulty paying attention") and 22 ("is distracted or has trouble functioning if there is a lot of noise around"), neither of which explicitly probes listening or even (in the case of Item 27) sound-related behavior but does clearly address attentional abilities. Negative behaviors on these items were also similarly elevated in Tomchek and Dunn's sample of children with ASD, with 79% responding "always/frequently" to Item 27 and 58% to Item 22.

No relationship was observed across the sample between auditory filtering scores and the other putative measures of CNS-mediated processing examined: cognition (FSIQ) and language function. The lack of correlation with IQ is consistent with previous studies, which reported that overall SSP scores are independent of IQ outcomes (Carr et al., 2010; Jirikowic et al., 2008). However, the lack of observed relationship across the sample between auditory filtering scores and language function is more surprising but is potentially related to the aggregate nature of the data used to derive this measure. "Language" is a complex behavioral domain, and the relatively gross clinical rankings of language function in the data set (based on available clinical measures that differed depending on the examined age range) potentially lacked appropriate resolution to capture the impact of problematic, higher order auditory behaviors on language functioning, particularly in younger children. It is also possible, as suggested by our findings, that the relationship between atypical auditory filtering behaviors and language function is not apparent until children are old enough that higher order, more subtle aspects of language are expected to be mastered. For example, Thorne and colleagues (Thorne, 2017; Thorne & Coggins, 2016) have observed impaired cohesive referencing—which, in English, relies on correct use of the articles "a" and "the," two similar sounding terms that can require subtle auditory processing to discriminate—to be highly prevalent in older children with FASDs. If, as we suggest, degraded linguistic input due to impaired sound-in-noise listening processes (reviewed in Bronkhorst, 2015) makes it challenging to learn the fundamental linguistic rules (White-Schwoch et al., 2015) involved in functional use of these two terms, atypical auditory filtering behaviors may have an impact on language functioning that is not captured by a global clinical ranking of language function in younger children but reveals itself when children are older. Prospective research that systematically explores the relationship between auditory function in FASDs and more specific measures of language function, particularly those that rely on subtle auditory processing, and particularly in older children, is needed.

Potential Limitations

This study represents a preliminary step in investigating auditory dysfunction in children with FASDs using retrospective SSP auditory filtering data, clinical measures of CNS function, and caregiver-provided peripheral hearing information. These existing data served as expedient but imperfect proxies for more targeted, objective, and systematic assessments of suprathreshold listening abilities and prospective audiologic evaluations. Due to the observational nature of the data, it is possible that hearing loss in the sample was underreported and that the imprecise behavioral measures available representing sound-in-noise listening and language function obscured the observation of important relationships. Moreover, the subjective caregiver ratings on the SSP were susceptible to bias, as with any caregiver rating, although it is important to note the caregivers completed the SSP prior to their child's FASD diagnostic evaluation, so their responses were not biased by knowledge of their child's FASD diagnosis. Systematic, prospective investigation

Figure 3. Profile of caregiver ratings on Short Sensory Profile auditory filtering items across fetal alcohol spectrum disorder diagnoses (abbreviations [Astley, 2004]: fetal alcohol syndrome [FAS], partial FAS [PFAS], static encephalopathy/alcohol exposed [SE/AE], and neurobehavioral disorder/alcohol exposed [ND/AE]). The percentage of "always" or "frequently" ratings with respect to the described negative behavior was higher, across fetal alcohol spectrum disorder diagnoses, for items related to sound-in-noise listening (Items 23 and 26: black bars) than for items related to sound sensitivity/distractibility (Items 24 and 25: gray bars).



employing carefully controlled objective measures of sound-in-noise listening abilities, detailed audiologic assessment, and more targeted neuropsychological testing in children with FASDs, grouped by different age bands, is needed.

Conclusions and Future Directions

Results from this study indicate that, although children with FAS exhibit a higher-than-normal prevalence of hearing loss, it is listening difficulties in the absence of hearing loss, likely related to suprathreshold processing deficits, that are strikingly prevalent across the spectrum of fetal alcohol disorders. Such listening difficulties are impactful—affecting life function adversely and potentially contributing to lifelong difficulties with linguistic exchange and/or social interaction—and are likely widespread, given that prenatal alcohol exposure is the leading preventable cause of birth defects and intellectual and neurodevelopmental disabilities (Williams & Smith, 2015). The present results related to listening difficulties in FASDs point to the importance of systematic clinical assessment of this domain of functioning whenever prenatal alcohol exposure is part of the clinical profile of an individual being assessed, so that common and relevant impairment is not missed.

Although it is unclear whether listening difficulties in FASDs derive from the similar etiologies as listening difficulties observed in children with other neurodevelopmental disorders or in children presumed to be typically developing, the physiological bases of listening difficulties, in general, remain unclear (DeBonis, 2015; D. R. Moore, 2018). FASD offers a unique opportunity to explore their etiology relative to the involvement of a known and well-characterized teratogen, alcohol. The present results suggest an important role for attention-related processes in listening difficulties in children with FASDs. However, a detailed and systematic investigation of auditory dysfunction in FASDs is needed before firm conclusions are reached. It will be important to characterize auditory behavior and objectively assess suprathreshold listening abilities in FASDs, using detailed audiologic and psychoacoustic assays, along with advanced multimodal neuroimaging methods to assess the functional integrity of the auditory pathway—from periphery to cortex—in order to better parse out the physiological bases of auditory dysfunction from among the multitude of candidate auditory and cognitive processes. Although there are few evidence-

based interventions available to date to ameliorate listening difficulties related to suprathreshold deficits, enhanced understanding of the physiological underpinnings of auditory dysfunction will ultimately improve diagnoses and better inform therapy options available to these listeners.

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ALCOHOLISM CLINICAL & EXPERIMENTAL RESEARCH

Are Low-to-Moderate Average Alcohol Consumption and Isolated Episodes of Binge Drinking in Early Pregnancy Associated with Facial Features Related to Fetal Alcohol Syndrome in 5-Year-Old Children?

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Background: Fetal alcohol syndrome (FAS) typically is observed among individuals with high prenatal alcohol exposures (PAE), but exposure histories obtained in clinical diagnostic settings are often inaccurate. The present analysis used the Lifestyle During Pregnancy Study (LDPS) to assess the potential effects of low-to-moderate average weekly alcohol consumption and binge drinking in early pregnancy on facial features associated with FAS among children 5 years of age.

Methods: The analysis is a prospective follow-up study of 670 women and their children sampled from the LDPS cohort based on maternal alcohol consumption during pregnancy. The 4-Digit Code FAS Facial Photographic Analysis Software was used to measure the magnitude of expression of the 3 diagnostic facial features of FAS from standardized digital photographs. Logistic regression was used to estimate the odds of presenting with the FAS/partial fetal alcohol syndrome (PFAS) facial phenotypes relative to different patterns of prenatal alcohol exposure.

Results: Ten children presented with the FAS/PFAS facial phenotypes. None of the children sampled met the central nervous system (CNS) criteria for FAS or PFAS at age 5 years. All remained at risk for PFAS since some types of CNS dysfunction associated with this diagnosis may only be assessed at older ages. The FAS/PFAS facial phenotypes were 8.5-fold more likely among children exposed to an average of 1 to 4 drinks/wk and 2.5-fold more likely among children with a single binge exposure in gestational weeks 3 to 4 compared to children with no such exposures. The magnitude of expression of the FAS facial phenotype was significantly correlated with all other diagnostic features of FAS: growth deficiency, microcephaly, and measures of CNS dysfunction.

Conclusions: These findings suggest that low-to-moderate levels of PAE or isolated binge exposures may place some fetuses at risk for FAS/PFAS. Thus, conservative advice is still for women to abstain from alcohol consumption during pregnancy.

Key Words: Alcohol, Alcohol Binge Drinking, Pregnancy, Fetal Alcohol Syndrome, Fetal Alcohol Spectrum Disorders.

FETAL ALCOHOL SYNDROME (FAS) is a permanent birth defect and developmental disability caused by in utero exposure to alcohol. FAS is characterized by growth deficiency, a unique constellation of minor facial anomalies, and structural, neurological, or functional central nervous system (CNS) abnormalities (Astley and Clarren, 2000; Bertrand et al., 2004; Stratton et al., 1996). Not all individuals exposed to and damaged by prenatal alcohol exposure have FAS, the most involved diagnosis under the umbrella of fetal alcohol spectrum disorders (FASDs). Prenatal exposure to alcohol can also result in more subtle adverse effects and diagnoses. The growth, facial, and CNS abnormalities can all present along separate continua from mild to severe (Stratton et al., 1996).

A number of FASD diagnostic schemes have been posed and applied worldwide (Astley, 2004; Bertrand et al., 2004; Bower and Elliott, 2016; Cook et al., 2016; American Psychiatric Association, 2013; Hoyme et al., 2016). All promote an interdisciplinary approach to diagnosis and broadly agree that FASDs are characterized by growth, facial, and CNS abnormalities. But, the specific criteria

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used to define each diagnosis under the umbrella of FASDs do differ across the diagnostic systems (Astley, 2011; Astley et al., 2017; Coles et al., 2016). It should be noted that all schemes assess facial features for an FAS diagnosis since these features reflect anomalies in prenatal brain development. The current analysis used criteria as outlined in Astley (2004), also known as the 4-Digit Code. Briefly, these criteria require all of the following:

1. Growth deficiency: prenatal and/or postnatal height and/or weight at or below the 10th percentile;
2. Facial dysmorphia: all 3 of the following: (i) short palpebral fissure lengths (PFLs; less than or equal to third percentile); (ii) smooth philtrum (Rank 4 or 5 on the University of Washington Lip-Philtrum Guide); and (iii) thin upper lip (Rank 4 or 5 on the University of Washington Lip-Philtrum Guide);
3. Evidence of severe CNS structural, neurological, and/or functional abnormalities;
4. Prenatal alcohol exposure: a confirmed or unknown history of exposure. FAS can be diagnosed in the absence of a confirmed prenatal alcohol exposure history if the 3 facial features (as defined by the Rank 4 facial phenotypes in the 4-Digit Code) are present. Empirical evidence confirms the Rank 4 facial phenotypes are so highly specific to (caused only by) prenatal alcohol exposure. Its presence can be used to confirm exposure when an exposure history is unavailable (Astley, 2013).

The FAS facial phenotype is not simply present or absent. It presents along a clinically meaningful continuum from mild to moderate to severe (Astley and Clarren, 2000). The magnitude of expression of the FAS facial phenotype not only increases with increasing prenatal alcohol exposure, but also correlates significantly with increasing severity of growth deficiency, microcephaly, and CNS dysfunction (Astley, 2013). These significant correlations serve to validate a causal association between prenatal alcohol exposure and the growth, facial, and CNS abnormalities currently used to define FAS (Astley, 2013; Astley and Clarren, 2001).

FAS is typically observed among individuals with reportedly high prenatal alcohol exposures (PAE; ≥6 drinks/d or 5 to 6 drinks within a short period of time) (O'Leary and Bower, 2012), but exposure histories obtained in clinical diagnostic settings often are inaccurate. For example, the average reported exposure among 154 individuals diagnosed with FAS or partial fetal alcohol syndrome (PFAS) at the University of Washington FAS Diagnostic & Prevention Network (FASDPN) using the 4-Digit Code was 8 to 12 drinks per drinking occasion, 5 to 6 days per week (Astley, 2010). This average exposure pattern, however, spanned a wide range. At the low end of the range, 1 of every 14 children with FAS or PFAS had a reported exposure of no more than 1 drink/d. Are these 1 in 14 cases especially vulnerable to the adverse effects of prenatal alcohol exposure, or were their lower exposures inaccurately reported? The Lifestyle During Pregnancy Study (LDPS) (Kesmodel et al., 2010, 2012) provided just such a dataset that addressed this issue by collecting prenatal alcohol exposure history during early pregnancy and using standardized measures of growth, face, and CNS.

The LDPS has previously provided data on the association between low-to-moderate alcohol intake and alcohol binge drinking and neuropsychological development, including intelligence, attention, psychomotor function, executive function, and behavior (Bay et al., 2012; Kesmodel et al., 2010, 2012, 2013). The objective of the present analysis was to use the LDPS to assess the potential effects of low-to-moderate average weekly alcohol consumption and binge drinking in early pregnancy on facial features associated with FAS among children 5 years of age. Specifically, we (i) document the occurrence of the individual FAS facial features and overall FAS facial phenotype in the study sample; (ii) assess the association between prenatal alcohol exposure and the magnitude of expression of the FAS facial features and phenotype; and (iii) assess the association between the magnitude of expression of the FAS facial phenotype and other diagnostic features of FAS, including cognitive impact, reduced head circumference, and growth deficiency.

MATERIALS AND METHODS

Study Sample

This study was part of the LDPS, which has been described in detail elsewhere (Kesmodel et al., 2010, 2012). Briefly, the study is a prospective follow-up study based on a subsample from the Danish National Birth Cohort (DNBC; Olsen et al., 2001).

A total of 1,628 mother–child pairs participated in the follow-up. Inclusion was based on a stratified sample with oversampling of women with low-to-moderate alcohol intake and binge drinking (Kesmodel et al., 2010, 2012). Exclusion criteria were inability to speak Danish, impaired hearing or vision causing inability to complete the cognitive tests, multiple pregnancies, and congenital diseases likely to cause mental retardation (Kesmodel et al., 2010). Data collection for the follow-up study took place from September 2003 to June 2008 (Kesmodel et al., 2010).

Of the 1,628 participants' images available for measurement, 670 met the inclusion criteria for this study and had at least 1 of the 3 facial features measured (see details in Appendix).

Exposure Assessment

Information on alcohol intake during pregnancy was derived from the first prenatal DNBC interview. Among the subsample of women participating in the follow-up, the median week of gestation for completing the prenatal interview was 17 weeks (range: 7 to 39 weeks). During the interview, the women were asked about their average number of beers, glasses of wine, and glasses of spirits they currently consumed at the time of the interview over the course of a week, and based on this information, the total number of weekly drinks was calculated. These alcohol exposure questions have been shown to yield valid estimates of alcohol consumption throughout pregnancy (relative to other methods) and reliable information among pregnant Danish women (Kesmodel and Olsen, 2001). Information on binge drinking during pregnancy included data on the number of binge episodes (defined as intake of ≥5 drinks on a single occasion) and the timing (gestational week) of these episodes (Kesmodel, 2001) up until the time of the interview. A number of women

in the current sample reported 1 or more binge episodes during early weeks of pregnancy, although their average number of drinks per week at the time of interview was zero (Kesmodel et al., 2012). These women were classified accordingly as consuming zero average drinks per week during pregnancy, but with 1 or more previous binge episodes. The definition of a drink followed the definition from the Danish National Board of Health, with 1 standard drink being equal to 12 g of pure alcohol. The sampling stratification for average weekly consumption and binge consumption in the first trimester has been described previously (Kesmodel et al., 2010, 2012). This stratification resulted in 5 sampling categories used in this analysis.

Outcome Measures

Facial Features. The follow-up assessments were conducted at 4 sites located in Copenhagen, Aarhus, Odense, and Aalborg. The assessment comprised a comprehensive neuropsychological test battery which is described in detail elsewhere (Kesmodel et al., 2010, 2012).

Following the test session, standardized digital facial photographs were taken of each mother and child to allow subsequent measurement of (dysmorphic) facial features, including the philtrum, the upper lip, and PFL. Specific procedures for taking and coding photographs are described in Appendix. All testers were blind to the exposure status of the participants, and all tests were administered in Danish.

Briefly, the University of Washington FAS Facial Photographic Analysis Software (Astley, 2016) was used to measure the magnitude of expression of each of the 3 diagnostic facial features of FAS (short PFLs: 2 or more standard deviations (SD) below the mean; smooth philtrum (Rank 4 or 5 on the University of Washington Lip-Philtrum Guide) and thin upper lip (Rank 4 or 5 on the Lip-Philtrum Guide (Fig. 1), lip circularity ≥75.5) as defined by the University of Washington FASD 4-Digit Code (Astley, 2016). For the 366 children with photographs of sufficient quality to allow accurate measurement of all 3 facial features, the magnitude of expression of the overall FAS facial phenotype (Face Rank) was ranked on a 4-point Likert scale (Rank 1: normal phenotype; Rank 2: mild FAS phenotype; Rank 3: moderate FAS phenotype; and Rank 4: severe FAS phenotype) in accordance with the FASD 4-Digit Code (Astley, 2004). The Scandinavian PFL growth charts (Stromland et al., 1999) and University of Washington Lip-Philtrum Guide 1 were used for this Danish population.

Cognitive Function. Child intelligence was assessed using the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) (Wechsler, 1990) covering the age span 3 to 7 years. The WPPSI-R includes 5 verbal and 5 performance subtests that are used to calculate an overall verbal intelligence quotient (VIQ), overall performance IQ (PIQ), and full-scale IQ (FSIQ). In this test battery, only 3 of the verbal (arithmetic, information, and vocabulary) and 3 of the performance (block design, geometric design, and object assembly) subtests were carried out to facilitate the child's cooperation throughout the testing. Standard procedures were used to prorate scores from the shortened test.

Child attention was assessed with the Test of Everyday Attention for Children at Five (TEACh-5; Underbjerg et al., 2012, 2013) covering the age span 5 years to 5 years and 3 months. For this study, 2 subtests assessing selective attention ("Great Balloon Hunt" and "Hide and Seek II") and 2 subtests assessing sustained attention ("Barking" and "Draw a line") were used. Each subtest score was standardized to a mean of 0 and a SD of 1. To calculate composite scores for overall, selective, and sustained attention, the means of the respective standardized subtest scores for each individual were calculated and restandardized to a mean of 0 and SD of 1.

Executive function was assessed using the Behavior Rating Inventory of Executive Function (BRIEF) questionnaire (Gioia et al., 2000) covering the age span 5 to 18 years. The questionnaire consists of 2 versions, 1 for parents and 1 for teachers. The parent version was used for these analyses because of higher participation. Each questionnaire evaluates 8 domains of executive functioning and forms the Global Executive Composite (GEC). Three of the 8 domains form the Behavioral Regulation Index (BRI), and 5 of the domains form the Metacognition Index (MI). Since the 8 domains do not follow a normal distribution, we performed a normalizing *t*-score transformation to standardize each domain to a mean of 50 and SD of 10. To compute the GEC, BRI, and MI, the means of the respective domains for each individual were calculated and restandardized to a mean of 50 and SD of 10. For all BRIEF scores, a higher score indicates more executive function difficulties.

Covariates

Factors demonstrated in previous research to influence child neurodevelopment were selected as covariates. The following covariates were obtained in the prenatal interview and subsequently coded as follows: parity (0, 1, ≥2); prenatal smoking (yes/no); and maternal prepregnancy body mass index (BMI) (weight in kg/[height in m]^2). At the time of the 5-year follow-up, the following variables were recorded: maternal marital status (single at either the prenatal interview or follow-up/with partner at both times) and parental education in years (total duration of attained education averaged for both parents or maternal only if information on the father was missing). Additional information on collection of covariate information is provided elsewhere (Kesmodel, 2012; Kesmodel et al., 2010).

Maternal age was obtained from the unique Danish personal identification number, as were sex and age of the child. Birthweight in grams, head circumference, and gestational age in days were obtained from the Danish Medical Birth Registry (Bliddal et al., 2018).

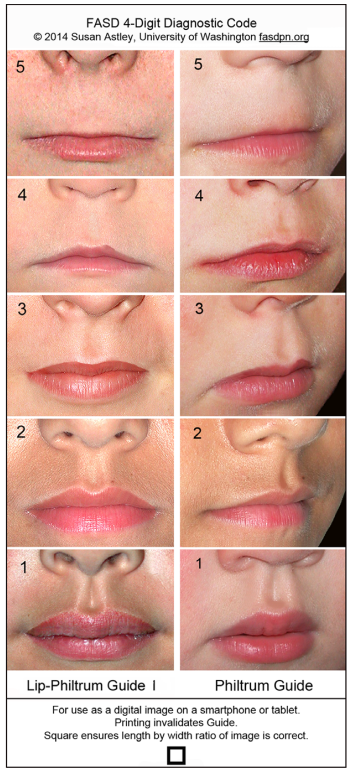
Data Analysis

Descriptive statistics (i.e., means, SDs, and proportions) were used to profile the sociodemographics of the study population, the maternal drinking patterns, and the magnitude of expression of the FAS facial features and phenotype. Logistic regression was used to document the odds of presenting with the FAS/PFAS facial phenotype (Face Rank 3 or 4), short PFLs (ABC-Score = C, 2 or more SDs below the mean), smooth philtrum (Rank 4 or 5), or thin upper lip (Rank 4 or 5) relative to 4 different patterns of prenatal alcohol exposure: (i) average number of drinks/week during pregnancy (0, 1 to 4, ≥5), (ii) binge drinking (yes/no), (iii) number of binge drinking episodes (0, 1, 2 ≥ 3), and (iv) gestational timing of the single binge drinking episode (no binge, weeks 1 to 2, weeks 3 to 4, weeks 5+; multiple episodes). Odds ratios were adjusted for predefined covariates (parity; prenatal smoking; maternal prepregnancy BMI; maternal marital status; parental education in years; maternal age at the birth of the index child; sex and age of the child).

Not all photographs were of sufficient quality (e.g., facial expression, rotation, and focus) to generate accurate measures of all 3 facial features. As a result, participants were divided into 2 groups. Group A (N = 366) consisted of children whose photographs were of sufficient quality to measure all 3 facial features. Group B (N = 670) consisted of children whose photographs were of sufficient quality to measure 1 to all 3 of the facial features. Group A is a subset of Group B. Group B was used for analyses focused on the individual facial features. Group A was used for analyses focused on the overall facial phenotype.

All analyses were conducted in SAS and Stata 12 (StataCorp LP, College Station, TX, USA) and weighted by sampling probabilities. Statistical tests were 2-sided and deemed significant at the 5% level. Estimates are accompanied by 95% confidence intervals.

A



B

Guide 1 Tables

Lip Rank	Lip Circularity Pictured	Lip Circularity Range
5	178	≥ 131.5
4	85	75.5 to 131.4
3	65	57.5 to 75.4
2	50	42.5 to 57.4
1	35	≤ 42.4

FACE TABLES

5-Point Rank for Philtrum or Lip	Z-scores for Palpebral Fissure Length	ABC-Scores for: Palpebral Fissure	Philtrum	Upper Lip
4 or 5	≤ - 2 SD	C	C	C
3	> -2 SD and ≤ -1 SD	B	B	B
1 or 2	> -1 SD	A	A	A

4-Digit Diagnostic Rank	Level of Expression of FAS Facial Features	Palpebral Fissure – Philtrum – Lip ABC-Score Combinations
4	Severe	CCC
3	Moderate	CCB, CBC, BCC
2	Mild	CCA, CAC, CBB, CBA, CAB, CAA BCB, BCA, BBC, BAC ACC, ACB, ACA, ABC, AAC
1	None	BBB, BBA, BAB, BAA ABB, ABA, AAB, AAA

GROWTH TABLES

Percentile Range	ABC-Scores for: Height	Weight
≤ 3rd	C	C
> 3rd and ≤ 10th	B	B
> 10th	A	A

4-Digit Diagnostic Rank	Growth Deficiency Category	Height-Weight ABC-Score Combinations
4	Severe	CC
3	Moderate	CB, BC, CA, AC
2	Mild	BA, BB, AB
1	None	AA

Fig. 1. (**A**) University of Washington Lip-Philtrum Guide 1 used to rank lip thinness and philtrum smoothness on 5-point Likert scales. (**B**) The face tables on the backside of the Lip-Philtrum Guide outline how the magnitude of expression of the FAS facial phenotype is ranked on a 4-point scale (Rank 1: normal; Rank 2: mild; Rank 3: moderate; and Rank 4: severe) (Astley, 2004). Copyright Susan Astley Hemingway. Reprinted by permission.

RESULTS

Sample Characteristics

Although the 2 subsets, Group A and Group B, were not randomly selected from the 1,628, the sociodemographic profiles (Table 1) and maternal drinking patterns (Table 2) confirm that both subgroups were highly reflective of one another and highly representative of the 1,628 participants from which they were drawn. Of the 366 women in Group A, 308 (84%) reported, on average, low-to-moderate alcohol consumption with isolated episodes of binge drinking, and 58 reported no alcohol consumption during pregnancy. Of the 670 women in Group B, 561 (84%) reported, on average, low-to-moderate alcohol consumption with isolated episodes of binge drinking, and 109 reported no alcohol consumption during pregnancy (Table 2).

Occurrence of the FAS and PFAS Facial Phenotypes

Among the 366 participants with all 3 facial features measured, 308 had confirmed exposure to alcohol. Nine of the 308 (2.9%) met the 4-Digit Code criteria for the moderate

Table 1. Sample Characteristics of the Current Study Populations and the Original LDPS Population from Which They Were Drawn

	LDPS 2012 study participants Mother and child pairs from alcohol sampling categories 1 to 5	Current 2018 study participants Children from the LDPS with	
		Group A All 3 facial features measured	Group B 1 to 3 facial features measured
Sample characteristics			
n	1,628	366	670
Sampling fraction (median, 10th/90th percentile)	9.7 (1.5/49.6)	9.7 (1.5/49.6)	9.7 (1.2/49.6)
Timing of interview, gestational week (median, 10th/90th percentile)	17 (13/24)	17 (13/23)	17 (13/23)
Family characteristics			
Maternal age, years (mean ± SD)	30.9 ± 4.4	30.9 ± 4.3	30.9 ± 4.3
Parity			
0 (%)	50.1	48.9	49.1
1 (%)	32.2	31.7	32.1
≥2 (%)	17.8	19.4	18.8
Maternal BMI (before pregnancy), kg/m^2 (median, 10th/90th percentile)	22.6 (19.6/28.7)	22.5 (19.7/29.3)	22.6 (19.6/29.1)
Maternal marital status: single (%)	12.1	12.0	11.0
Parental education, years (median, 10th/90th percentile)	13.0 (11.0/16.0)	12.5 (11.0/16.0)	13.0 (11.0/16.0)
Family home index: suboptimal (%)	18.7	20.8	18.6
Maternal IQ (mean ± SD)	100.0 ± 15.0	100 ± 14.8	
Maternal smoking during pregnancy (%)	31.4	33.9	32.2
Parental postnatal smoking (%)	31.9	33.3	31.1
Maternal binge drinking in pregnancy (%)	69.6	70.8	67.6
Median number of drinks per week during pregnancy (median, 10th/90th percentile)	0.5 (0/5)	0.5 (0/5)	0,5 (0/5)
Child characteristics			
Male sex (%)	52.0	46.5	48.5
Age at testing, years (median, 10th/90th percentile)	5.2 (5.1/5.3)	5.2 (5.1/5.3)	5.2 (5.1/5.3)
Birthweight, grams (mean ± SD)	3601.9 ± 516.1	3,600 ± 507.3	3613.6 ± 521.4
Gestational age, days (median, 10th/90th percentile)	281 (267/293)	281 (267/293)	282 (269/293)
Medical condition or medication (%)	3.3	1.6	2.4
Impaired hearing abilities (%)	4.7	4.4	4.8
Impaired vision abilities (%)	2.9	2.5	2.7

expression of the FAS facial phenotype (Face Rank 3), and 1 (0.3%) met the criteria for the severe expression of the FAS facial phenotype (Face Rank 4) (Table 3). Measures of growth, CNS structure and function, and maternal drinking patterns are presented in Table 4 to document whether any of these 10 children met the diagnostic criteria for FAS or PFAS in accordance with the FASD 4-Digit Code. All children were alcohol-exposed. Their mothers reported an average intake of 0 to 7 drinks/wk before pregnancy, 0 to 2 drinks on average per week during pregnancy, and a maximum of 1 binge episode during the first 20 weeks of pregnancy. All children were born at term. Five of the 10 presented with growth, head circumference, and/or IQ measures between 1 and 2 SDs below the mean. None of the children presented with growth measures at or below the 10th percentile. One child presented with a head circumference at the 10th percentile. In the absence of microcephaly (head circumference less than or equal to third percentile), FAS and PFAS require evidence of brain dysfunction. The level of brain dysfunction required for FAS or PFAS (CNS Rank 3) is defined by the 4-Digit Code as 3 or more domains of brain function, 2 or more SDs below the mean based on a comprehensive assessment of language, memory, executive function, cognition, motor, attention, and adaptation, using validated instruments administered by clinical professionals (Astley, 2004). To confirm or rule out this level of brain dysfunction, these assessments must be administered when a child is old enough (typically >8 years) to engage in assessments of more complex, mature brain function (Astley, 2004). None of the 10 children met the above criteria for brain dysfunction based on the WPPSI-R IQ test. Thus, at 5 years of age, none of the 10 children met the 4-Digit Code CNS criteria for FAS or PFAS, but all remain at risk for PFAS because CNS dysfunction (CNS Rank 3) cannot be confirmed or ruled out at this young age.

Among the 304 children in which only 1 or 2 facial features could be measured, the full FAS facial phenotype (Face Rank 4) could effectively be ruled out in 96% and the moderate expression of FAS facial phenotype (Face Rank 3) could be ruled out in 77%. When combined with the facial outcomes of the 366 children with all 3 facial features measured, the FAS/PFAS facial phenotypes (Face Ranks 3 to 4) could be ruled out in 96.7% of the 670 children.

Table 2. Distribution of Maternal Drinking Patterns in the Original LDPS 2012 Study and the Current 2018 Study

Average standard drinks per week	Binge[a] drinking				LDPS 2012[b]	Current 2018 Facial Study	
	Gestational weeks				Participants	Group A All 3 facial features measured	Group B 1 to 3 facial features measured
During pregnancy	1 to 2	3 to 4	5 to 8	≥9	*N* = 1,622 *N*	*N* = 366 *N* (% of LDPS)	*N* = 670 *N* (% of LDPS)
0	No	No	No	No	257	58 (23)	109 (42)
0	Yes	No	No	No	113	28 (25)	47 (42)
0	No	Yes	No	No	104	25 (24)	42 (40)
0	No	No	Yes	No	109	24 (22)	55 (50)
0	No	No	No	Yes	94	21 (22)	38 (40)
					Total 677	Total 156 (23)	Total 291 (43)
1 to 4	No	No	No	No	155	30 (19)	72 (46)
1 to 4	Yes	No	No	No	113	30 (27)	43 (38)
1 to 4	No	Yes	No	No	120	23 (19)	43 (36)
1 to 4	No	No	Yes	No	93	28 (30)	45 (48)
1 to 4	No	No	No	Yes	114	21 (18)	39 (34)
					Total 595	Total 132 (22)	Total 242 (41)
0	Yes in at least 2				81	21 (26)	33 (41)
1 to 8	Yes in at least 2				82	15 (18)	28 (34)
	1 to 2	3 to 4	≥5		Total 163	Total 36 (22)	Total 61 (37)
5 to 8	No	No	No		79	17 (22)	35 (44)
5 to 8	Yes	No	No		11	1 (9)	1 (9)
5 to 8	No	Yes	No		37	7 (19)	15 (41)
5 to 8	No	No	Yes		40	12 (30)	18 (45)
≥9	No	No	No		15	4 (27)	5 (33)
≥9	Yes in at least 2				5	1 (20)	2 (40)
					Total 187	Total 42 (22)	Total 76 (41)
No. of binge drinking episodes during pregnancy							
				0	495	107 (22)	217 (44)
				1	783	182 (23)	312 (40)
				2	225	47 (21)	95 (42)
				3 to 12	114	30 (26)	46 (40)

[a]Defined as an intake of 5 or more standard drinks on one occasion.
[b]Lifestyle During Pregnancy Study 2012.

Occurrence of the Individual FAS Facial Features

Among the 670 participants with 1, 2, or all 3 of the facial features measured, 4% presented with PFLs 2 or more SDs below the mean (PFL ABC-Score = C), 11% presented with moderately-to-completely smooth philtrums (Philtrum Ranks 4 and 5; ABC-Score = C), and 41% presented with moderately-to-severely thin upper lips (Lip Ranks 4 and 5; ABC-Score = C; Table 3; Fig. 1). The prevalence of each FAS facial feature was nearly identical in the smaller subset of 366 participants that had all 3 facial features measured.

Association Between FAS/PFAS Facial Features and Prenatal Alcohol Exposure

Table 5 shows the odds of presenting with the FAS/PFAS facial phenotypes (Face Rank 3 or 4) across different patterns of quantity, frequency, and timing of prenatal alcohol exposure. Exposure to 1 to 4 drinks/wk on average during gestation was associated with a significant 8.5-fold increased odds for presenting with the FAS/PFAS facial phenotypes compared to participants with no average drinks per week. Exposure to a single binge drinking episode was associated with a significant 1.9-fold increased odds for the FAS/PFAS facial phenotypes. When the timing of the single binge exposure was in gestational weeks 3 to 4, participants were 2.5-fold more likely to present with the FAS/PFAS facial phenotypes than participants with no binge exposure. Single binge exposures occurring before or after gestational weeks 3 to 4 did not result in a significantly increased odds of the FAS/PFAS facial phenotypes.

Table 5 also presents the odds of presenting with each of the individual facial features of FAS (short PFL: ≤−2 SDs, ABC-Score = C), smooth philtrum (Rank 4 or 5, ABC-Score = C), and thin upper lip (Rank 4 or 5, ABC-Score = C) across the different patterns of prenatal alcohol exposure.

PFL. The odds of presenting with short PFLs (ABC-Score = C) increased significantly from 1.8-fold to 3.7-fold as the average number of drinks per week during pregnancy increased from 1 to 4 to ≥5. The odds of short PFLs increased significantly as the timing of binge exposure

Table 3. Distribution of the FAS Facial Features in the 2 Study Populations

	Group A All 3 facial features measured *N* (valid %)	Group B 1 to 3 facial features measured *N* (valid %)
Number of facial features measured[a]	Total *N* = 366	Total *N* = 670
Only 1	0 (0%)	102 (15%)
2 of the 3	0 (0%)	202 (30%)
All 3	366 (100%)	366 (55%)
FAS face rank		
Normal: Rank 1	172 (47%)	172
Mild: Rank 2	184 (50%)	184
Moderate: Rank 3	9 (2%)	9
Severe: Rank 4	1 (< 1%)	1
Among the 304 with only 1 or 2 features measured[b]		Total *N* = 304
Rank 1 ruled out	N/A	12 (4%)
Rank 4 ruled out	N/A	38 (12%)
Ranks 1 and 4 ruled out	N/A	20 (7%)
Ranks 3 and 4 ruled out	N/A	211 (69%)
Ranks 1, 3, and 4 ruled out	N/A	23 (8%)
PFL	Total *N* = 366	Total *N* = 491
ABC-Score[c]		
A (>−1 SD)	298 (81%)	411 (84%)
B (>−2 SDs & ≤−1 SD)	50 (14%)	58 (12%)
C (≤−2 SDs)	18 (5%)	22 (4%)
Philtrum smoothness		
ABC-Score[c]	Total *N* = 366	Total *N* = 648
A (Rank 1 or 2)	152 (41%)	261 (40%)
B (Rank 3)	168 (46%)	314 (49%)
C (Rank 4 or 5)	46 (13%)	73 (11%)
5-Point Rank[c]	Total *N* = 366	Total *N* = 648
1 (deeply grooved)	30 (8%)	54 (8%)
2 (moderately grooved)	122 (33%)	207 (32%)
3 (normal groove)	168 (46%)	314 (48%)
4 (moderately smooth)	42 (11%)	69 (11%)
5 (very smooth)	4 (1%)	4 (1%)
Upper lip thinness		
ABC-Score[c]	Total *N* = 366	Total *N* = 465
A (Rank 1 or 2)	75 (20%)	102 (22%)
B (Rank 3)	130 (36%)	174 (37%)
C (Rank 4 or 5)	161 (44%)	189 (41%)
5-Point Rank[c]	Total *N* = 366	Total *N* = 465
1 (very thick)	8 (2%)	11 (2%)
2 (moderately thick)	67 (18%)	91 (20%)
3 (normal thickness)	130 (36%)	174 (37%)
4 (moderately thin)	135 (37%)	161 (35%)
5 (very thin)	26 (7%)	28 (6%)

[a]The quality of a child's photoset did not always allow all 3 facial features to be measured.
[b]Even though only 1 or 2 facial features could be measured, the outcome of those features allowed 1 or more Face Ranks to be ruled out.
[c]See Fig. 1.

occurred earlier in gestation. The odds were highest when binge(s) occurred in weeks 1 to 2 and lowest when binge(s) occurred during or after gestational week 5, although not statistically significant. The odds of short PFLs was highest with a single binge exposure and significantly lower with 2 or more binge episodes.

Philtrum. Odds of a smooth philtrum (ABC-Score = C) appeared to be more dependent on the timing of binge exposure than the number of binge exposures. The odds were significant and highest (1.3-fold higher) when binge drinking occurred in weeks 1 to 2. Odds decreased linearly as binge drinking occurred later in gestation. Intake of 1 to 4 drinks/wk on average and 2 binge episodes in early pregnancy were associated with significantly lower odds of a smooth philtrum.

Lip. Odds of upper lip thinness (ABC-Score = C) also appeared to be more dependent on the timing of binge exposure rather than the number of binge exposures. Participants with 1 binge exposure were at significantly higher odds (Odds ratios [OR] 1.19) for thin upper lip than participants with no binge exposures. When binge exposure occurred in weeks 3 to 4, odds of a thin upper lip was greatest (OR 1.66). When binge exposure occurred in week 5 or later, children were significantly less likely to present with a thin upper lip (OR 0.83).

Associations Between the Magnitude of Expression of the FAS Facial Phenotype and Other Diagnostic Features of FASD

Individuals with short PFLs (≤−2 SDs) had significantly lower mean FSIQ and PIQ scores (5 to 7 points lower) than

Table 4. Characteristics of the 10 Children With Rank 3 or Rank 4 FAS Facial Phenotypes. Growth[a] and Neuropsychological[b] Outcomes Provided in Terms of Deviation From the Mean in Standard Deviations Using Standardized Norms

Child			Maternal					Child									
			Average alcohol intake drinks per week		Alcohol binge episodes			At birth					At 5 years of age				
Face Rank	Sex	Planned pregnancy	Before pregnancy	During pregnancy	Number	Timing: gestational weeks	Gestational age[c]	Birthweight	Length at birth	Head circumference at birth	Weight at age 5	Height at age 5	Head circumference at age 5	IQ at age 5	TEACh (overall attention, mean)	BRIEF (GEC mean)
3	Male	Yes	0.0	0.0	1	9+	39	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*
3	Male	Yes	0.0	0.0	1	9+	40	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	−1.9 SD; −1 SD
3	Male	Yes	0.5	0.5	0		41	*N*	*N*	*N*	*N*	*N*	*N*	1 SD; 1.9 SD	*N*	*N*
3	Female	No	0.5	0.5	1	1 to 2	40	−1.9 SD; −1 SD	*N*	*N*	*N*	*N*	*N*	*N*	−1.9 SD; −1 SD	*N*
3	Male	Yes	3.0	0.0	1	3 to 4	40	*N*	*N*	*N*	*N*	*N*	−1.9 SD; −1 SD	*N*	1 SD; 1.9 SD	*N*
3	Female	Yes	3.0	2.0	0		41	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*	*N*
3	Female	Yes	4.0	0.5	1	3 to 4	39	−1.9 SD; −1 SD	*N*	*N*	*N*	*N*	*N*	−1.9 SD; −1 SD	*N*	−1.9 SD; −1 SD
3	Male	No	6.0	0.0	1	5 to 8	39	*N*	*N*	*N*	1 SD; 1.9 SD	1 SD; 1.9 SD	*N*	*N*	*N*	*N*
3	Male	Yes	7.0	0.0	1	1 to 2	40	*N*	*N*	*N*	−1.9 SD; −1 SD	*N*	−1.9 SD; −1 SD	*N*	−1.9 SD; −1 SD	*N*
4	Female	Yes	1.0	0.5	1	3 to 4	39	−1.9 SD; −1 SD	*N*	*N*	1 SD; 1.9 SD	1 SD; 1.9 SD	*N*	*N*	*N*	*N*

[a]Anthropometric measures originally reported in grams (birthweight), kg (weight at age 5 years), or cm (length at birth, height at age 5 years, head circumference at birth and at age 5 years). Presented as deviations from the mean in SD (Danish standard growth curves) in order to avoid identification of individuals.
[b]FSIQ measured with WPPSI-R on standard IQ-scale (mean of 100, SD = 15). Attention measured with TEACh-5 (Test of Everyday Attention for Children at Five). Executive function measured with BRIEF (Behavior Rating Inventory of Executive Function). Presented as deviations from the mean: *N* = −1 SD to +1 SD from population means to avoid identification of individuals.
[c]Calculated in days and converted to completed weeks as presentation in days potentially allows for identification of individuals.

the reference group with normal PFLs (>−1 SD) (Table 6). Individuals with smooth philtrums (Rank 4 or 5) had significantly lower mean FSIQ and VIQ scores (3 to 4 points lower) than individuals with deep philtrums (Rank 1 or 2). Individuals with thin upper lip (Rank 4 or 5) had a significantly higher mean VIQ score (2.5 points higher) than individuals with thicker upper lips (Ranks 1 and 2). When the 3 facial features were assessed together, individuals with the Rank 3 or 4 FAS/PFAS facial phenotypes presented with mean FSIQ and PIQ scores that were 4 to 7 points lower than the individuals with normal facial phenotypes (Ranks 1 and 2). Although the magnitude and direction of association were equivalent to those observed for the individual facial features, the contrasts were not statistically significant. The smaller sample sizes resulted in insufficient power (<80%) to identify the 4 to 7 point contrasts as statistically significant.

We found no significant or clinically relevant differences between children with different facial phenotypes or different measures of individual facial features and executive function and attention (data not presented).

Mean birthweight, birth length, and birth head circumference decreased significantly with increasing magnitude of expression of the FAS facial phenotype (Face Ranks 1 to 4) among the 366 participants in Group A (Fig. 2).

DISCUSSION

Summary

There were 3 core findings in this study with a sample of 670 children in which 109 had no prenatal alcohol exposure and 561 had low-to-moderate exposure with isolated binge episodes. First, 10 children presented with the FAS/PFAS facial phenotypes (Face Rank 3 or 4). All 10 were alcohol-exposed. None met the diagnostic criteria for FAS or PFAS at 5 years of age. All 10, however, remain at risk for PFAS because they were too young at age 5 years to engage in the battery of neuropsychological assessments required to confirm or rule out brain dysfunction. Second, children exposed to 1 to 4 drinks/wk were 8.5-fold more likely to present with the FAS/PFAS facial phenotypes (Rank 3 or 4) than children with no prenatal alcohol exposure. Risk of the FAS/PFAS facial phenotypes was also significantly increased (2.5-fold) among children with a single binge exposure in gestational weeks 3 to 4 compared to children with no binge exposures. And third, the magnitude of expression of the FAS facial phenotype was significantly correlated with all other diagnostic features of FAS: growth deficiency, microcephaly, and measures of CNS dysfunction, even if measures of these features were within the normal range in this sample.

A primary objective of this study was to determine whether adverse outcomes typically observed among populations with high PAE could be found in a population with much lower exposure. Since the facial features that define FAS/PFAS were measured using the same software (Astley, 2016), personnel, and FASD diagnostic system (Astley,

Table 5. Odds Ratios[a] for Dysmorphic Facial Features Among the 366 Children from GROUP A With all 3 Facial Features Measured and the 670 Children From Group B With 1 to 3 Facial Features Measured in Relation to Pattern of Maternal Alcohol Consumption During Pregnancy

Alcohol pattern	Face ranks 3 to 4 versus 1 to 2 *N* = 10 versus *n* = 356 From Group A: *N* = 366 OR (95% CI)	PFL ABC-Scores[b] C versus AB *N* = 22 versus *N* = 469 From Group B: *N* = 670 OR (95% CI)	Philtrum ABC-Scores[b] C versus AB *N* = 73 versus *N* = 575 From Group B: *N* = 670 OR (95% CI)	Upper lip ABC-Scores[b] C versus AB *N* = 189 versus *N* = 276 From Group B: *N* = 670 OR (95% CI)
Average number of drinks per week during pregnancy				
0	Reference	Reference	Reference	Reference
1 to 4	8.50 (6.03 to 12.0)	1.76 (1.42 to 2.16)	0.87 (0.79 to 0.96)	0.97 (0.90 to 1.05)
≥5	*No rank 3 to 4 faces in this category*	3.71 (2.15 to 6.40)	0.76 (0.47 to 1.24)	1.16 (0.85 to 1.58)
p-Value[c]	<0.001	<0.001	0.01	0.46
Binge drinking in pregnancy				
No	Reference[d]	Reference	Reference	Reference
Yes	1.36 (1.03 to 1.78)	0.85 (0.67 to 1.08)	0.92 (0.82 to 1.03)	1.08 (0.99 to 1.18)
p-Value	0.03	0.19	0.15	0.07
Number of binge drinking episodes in pregnancy				
0	Reference	Reference[c]	Reference	Reference
1	1.94 (1.48 to 2.54)	1.20 (0.94 to 1.54)	1.00 (0.87 to 1.14)	1.19 (1.08 to 1.31)
2	*No rank 3 to 4 faces in this category*	0.11 (0.03 to 0.35)	0.71 (0.57 to 0.89)	0.86 (0.74 to 0.99)
≥3	*No rank 3 to 4 faces in this category*	0.44 (0.21 to 0.96)	0.96 (0.70 to 1.31)	1.08 (0.87 to 1.35)
p-Value	<0.001	<0.001	0.02	0.93
Timing of binge drinking episodes in pregnancy (gestational week)				
No binge	Reference	Reference	Reference	Reference
Weeks 1 to 2 only	1.46 (0.90 to 2.35)	1.13 (0.76 to 1.69)	1.32 (1.08 to 1.62)	1.12 (0.95 to 1.31)
Weeks 3 to 4 only	2.47 (1.79 to 3.41)	1.10 (0.78 to 1.56)	0.91 (0.76 to 1.08)	1.66 (1.46 to 1.90)
Week ≥5 only	0.80 (0.43 to 1.49)	0.99 (0.66 to 1.48)	0.87 (0.69 to 1.08)	0.83 (0.71 to 0.98)
Multiple episodes	*No rank 3 to 4 faces in this category*	*No rank C PFLs in this category*	0.79 (0.62 to 1.01)	1.05 (0.89 to 1.24)
p-Value	<0.001	<0.001	0.007	<0.001

[a]OR adjusted for sociodemographic and sampling factors. 95% confidence intervals that do not span 1.0 are statistically significant at $p < 0.05$.
[b]Facial ABC-Scores from the FASD 4-Digit Code are defined in Fig. 1.
[c]*p*-Value for the hypothesis of no difference in facial fetaures across levels of alcohol intake.
[d]The reference groups have zero exposure only for the type of exposure pattern being assessed, but have the full range of exposure based on the other patterns. For example, this reference group of 109 participants has zero binge episodes of exposure, but 30 (28%) were exposed to an average of 1 to 4 drinks/wk during pregnancy and 21 (19%) were exposed to an average of 5 or more drinks/wk during pregnancy.

Table 6. Association Between Facial Features and Child IQ[a]

	Full-scale IQ (standard score)				Performance IQ (standard score)				Verbal IQ (standard score)			
Intelligence	Mean	Mean difference	95% CI	*p*-Value	Mean	Mean difference	95% CI	*p*-Value	Mean	Mean difference	95% CI	*p*-Value
Facial features measure[b]												
Facial phenotype rank												
Ranks 1 and 2 (N = 355)	106.7	Reference			107.4	Reference			104.8	Reference		
Ranks 3 and 4 (N = 10)	102.5	−4.2	−11.7, 3.3	0.269	100.6	−6.8	−16.6, 3.0	0.175	103.6	−1.2	−7.6, 5.3	0.724
PFL ABC-Score												
A (>−1 SD) (N = 410)	107.2	Reference			107.7	Reference			105.2	Reference		
B (>−2 SD & ≤−1 SD) (N = 57)	103.9	−3.3	−6.6, 0.06	0.055	102.4	−5.3	−9.6, −1.0	0.015	104.4	−0.9	−3.7, 2.0	0.553
C (≤−2 SD) (N = 22)	101.3	−5.9	−11.0, −0.7	0.025	100.4	−7.3	−13.8, −0.8	0.027	102.0	−3.2	−7.7, 1.3	0.160
Philtrum ABC-Score												
A (Rank 1 or 2) (N = 260)	107.8	Reference			107.9	Reference			106.1	Reference		
B (Rank 3) (N = 314)	105.5	−2.3	−4.4, −0.2	0.034	105.6	−2.2	−5.0, 0.5	0.115	104.3	−1.8	−3.6, −0.07	0.041
C (Rank 4 or 5) (N = 73)	104.1	−3.5	−6.9, −0.1	0.042	104.3	−3.4	−7.6, 0.8	0.116	103	−2.9	−5.8, −0.03	0.048
Upper Lip ABC-Score												
A (Rank 1 or 2) (N = 102)	105.9	Reference			107.3	Reference			103.4	Reference		
B (Rank 3) (N = 174)	106.0	0.1	−3.2, 3.4	0.950	106.7	−0.7	−4.9, 3.5	0.757	104.1	0.7	−2.0, 3.4	0.613
C (Rank 4 or 5) (N = 188)	107.2	1.3	−1.7, 4.3	0.388	106.9	−0.5	−4.4, 3.4	0.810	106.0	2.5	0.06, 5.0	0.045

PFL, palpebral fissure length.
[a]IQ measured with WPPSI-R.
[b]Face Ranks and ABC-Scores described in Fig. 1.

2004) used to measure facial features in the University of Washington FASDPN clinical population, relevant comparisons can be made between the 2 populations. The FASDPN dataset includes over 3,000 individuals with prenatal alcohol exposure who received an interdisciplinary FASD diagnostic evaluation using the FASD 4-Digit Diagnostic Code (Astley, 2010). The alcohol exposures reported in the current study population (83% reported no more than 1 to 8 drinks/wk and/or isolated binge episode [drinking categories 1a to 4c; Table 1]) were considerably lower than the alcohol exposures reported in the FASDPN clinical population (76% report greater than 1 to 8 drinks/wk; average exposure is 7 to 9 drinks per occasion, 4 to 5 d/wk) (Astley, 2010).

Prevalence of FAS Facial Features and Correlation with Prenatal Alcohol Exposure

In the current study population with low-to-moderate prenatal alcohol exposure, 3.2% (10/308) presented with the FAS/PFAS facial phenotypes (Rank 3 or 4). All were exposed to no more than 7 drinks/wk and no more than a single episode of binge drinking. In contrast, a much higher proportion of individuals (19%) present with the FAS/PFAS facial phenotypes in the FASDPN patient population (Astley, 2010). Although individuals in the FASDPN patient population are, on average, highly exposed, 1 of every 14 diagnosed with FAS/PFAS has a reported exposure of no more than 7 drinks/wk. This is similar to the 10 children with the FAS/PFAS facial phenotypes in the current study. Although prenatal alcohol exposure may have been underreported for these 1 in 14 cases, it is also possible that these children are particularly vulnerable to lower levels of exposure. Future research may want to examine this possibility. The outcomes in the current study suggest that lower exposures may, in fact, be sufficient to produce the FAS/PFAS facial phenotypes in a small proportion of children. Timing of exposure also appears to be important. Perhaps one of the most compelling findings in the current study was a significant 2.5-fold increased odds of the FAS/PFAS facial phenotypes among children with a single binge exposure in gestational weeks 3 to 4. Gestational weeks 3 and 4 reflect the primitive streak and gastrulation stage of embryogenesis—a critical period of induction of alcohol-induced craniofacial alterations (Astley, 2013; Astley et al., 1999; Sulik, 1984).

FAS and PFAS require more than just the Rank 3 or 4 facial phenotype. Although 10 children in the current study presented with the Rank 3 or 4 FAS/PFAS facial phenotypes, none met the diagnostic criteria for FAS or PFAS (in accordance with the 4-Digit Code) at the young age of 5 years. FAS is defined by growth ≤10th percentile, a Rank 4 facial phenotype, and microcephaly (less than or equal to third percentile) and/or brain dysfunction (3 or more domains of brain function 2 or more SDs below the mean) (Astley, 2004). PFAS is defined by normal growth,

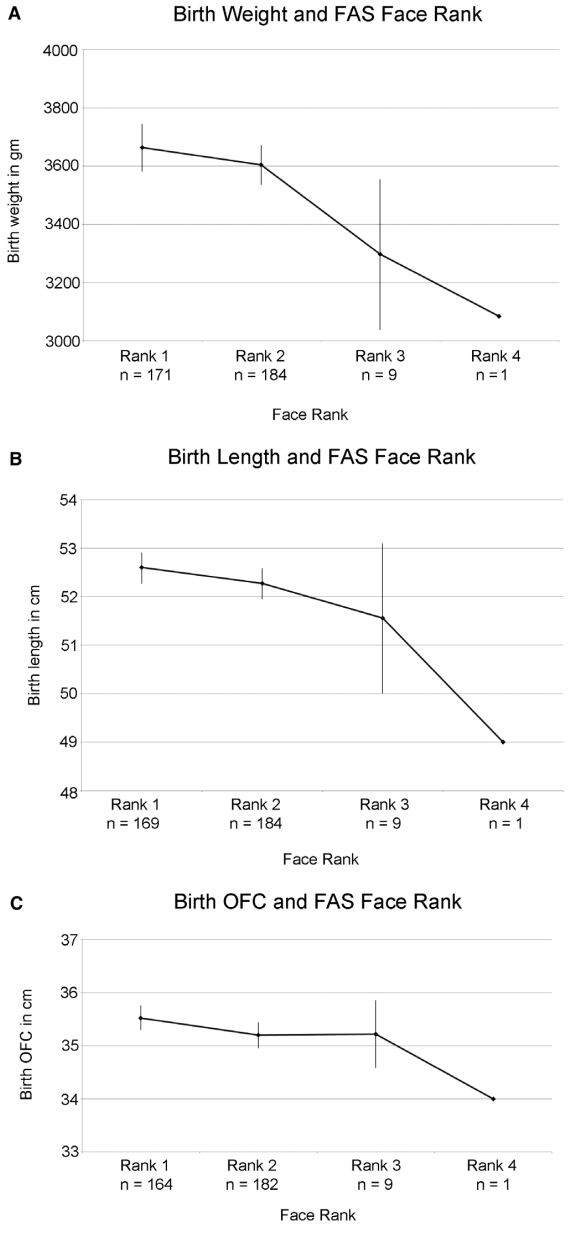


Fig. 2. Mean birthweight, birth length, and birth head circumference decreased significantly with increasing magnitude of expression of the FAS facial phenotype (Face Ranks: 1, normal; 2, mild; 3, moderate; and 4, severe) among the 366 participants in Group A. Error bars reflect 95% CIs. One-way ANOVA test for linear trend *p*-values: birth length 0.04, and birthweight and head circumference 0.001.

a Rank 3 or 4 facial phenotype, and microcephaly and/or brain dysfunction (3 or more domains of brain function 2 or more SDs below the mean). Since no child presented with growth ≤10th percentile, no child met the criteria for FAS. In contrast, all 10 children met the growth and facial criteria for PFAS. None of them presented with microcephaly; therefore, CNS dysfunction would be required to meet the CNS criteria for PFAS. Nevertheless, at 5 years of age, all were too young to participate in the battery of assessments required to confirm or rule out CNS dysfunction. As documented in the FASDPN clinical population, most children with FAS or PFAS do not present with severe brain dysfunction until later in childhood. For example, among 87 children ≤5 years of age at the time of their FAS/PFAS diagnosis at the FASDPN, only 24% met the criteria for severe CNS dysfunction (3 or more domains of function 2 or more SDs below the mean). Among 152 children >5 years of age at the time of their FAS/PFAS diagnosis, 84% met the criteria for severe CNS dysfunction. In addition, recent research (Astley et al., 2016) documents that 67 and 70% of young children with prenatal alcohol exposure that present with the Rank 3 or 4 FAS facial phenotypes, respectively, will present with severe CNS dysfunction (3 or more domains of brain function 2 or more SDs below the mean) when they are old enough (>8 years of age) to engage in more sophisticated assessments of brain function. Thus, if any of the 10 children with the Rank 3 or 4 FAS/PFAS facial phenotypes present with brain dysfunction (3 or more domains of brain function 2 or more SDs below the mean) later in childhood, they would meet the diagnostic criteria for PFAS.

Prenatal alcohol exposure was significantly correlated with the FAS facial phenotype and the 3 individual features that comprise the FAS facial phenotype. The strongest correlations with alcohol (ORs of 1.9 to 8.5) were observed when the 3 features appeared together to produce the Rank 3 or 4 FAS/PFAS facial phenotypes (Table 5). Since the Rank 4 FAS facial phenotype is confirmed to be highly specific to prenatal alcohol exposure (Astley, 2013; Astley and Clarren, 1996), it is highly likely that the FAS/PFAS facial phenotypes observed in these 10 children were caused by their prenatal alcohol exposure. Weaker, but statistically significant, correlations (ORs of 1.2 to 3.7) were observed between prenatal alcohol exposure and each individual FAS facial feature. This would be expected since alcohol is not the only factor influencing the length of a palpebral fissure, the depth of a philtrum, or the thickness of an upper lip. Perhaps one of the strongest factors other than alcohol influencing the physical presentation of these 3 facial features is familial genetics. A unique strength of the current study was the opportunity to measure the birth mothers' facial features. Among the 10 children who presented with the Rank 3 or 4 FAS facial phenotypes, all of their birth mothers presented with normal facial phenotypes (Face Ranks 1 and 2).

Correlations Between the FAS Facial Phenotype and Growth Deficiency, Microcephaly, and CNS Dysfunction

The correlations between face, growth, and CNS abnormalities observed in the current study (Fig. 2) are nearly

identical to those documented in the FASDPN clinical population (figures 8 and 9 in Astley, 2013). This study extends understanding of these correlations to a population of children with low-to-moderate prenatal alcohol exposure.

Strengths

The sample of women and children used for this study form part of a well-described, prospective cohort (Kesmodel et al., 2010; Olsen et al., 2001). While information bias is always a potential problem in observational studies (Kesmodel, 2018), the risk of information bias was minimized. Information on alcohol drinking patterns was collected directly from the birth mothers during pregnancy using validated instruments (Kesmodel, 2001; Kesmodel and Olsen, 2001), and all facial measures were performed by the inventor of the software system (Astley, 2016) used in this paper, thereby eliminating any interobserver variability and reducing the likelihood of measurement error. Further, facial measurements were taken blind to the child's exposure history. Because of the detailed information available on all participants, confounding could be addressed by adjusting for a priori selected potential confounders (Howards, 2018), following the same criteria as previous papers based on this cohort (Kesmodel et al., 2012). Also, it has previously been shown that despite selection problems in the DNBC, the external validity of measures of association seems to be good (Nohr and Liew, 2018).

Weaknesses

The DNBC represents only approximately 30% of all Danish pregnant women and hence is not a representative sample (Olsen et al., 2001). Further, the LDPS sample is a stratified sample within the DNBC (Kesmodel et al., 2010), making the current sample even less representative of the background population. While such selection may make the sample less suitable for firm statements about the overall prevalence of specific traits, inferences based on measures of association have been shown to be valid within the cohort (Nohr and Liew, 2018). Finally, since only 10 children presented with the Rank 3 to 4 facial phenotypes, the representativeness of this small group may be limited, but the statistical power was sufficient to identify significant associations with level and timing of prenatal alcohol exposure.

CONCLUSION

In conclusion, we found that approximately 3% (10/308) of the children whose mothers reported low-to-moderate alcohol intake, not usually associated with the full FAS, met the criteria for moderate-to-severe expression of the FAS facial phenotypes, Face Ranks 3 to 4. None met the diagnostic criteria for FAS or PFAS at 5 years of age. However, all 10 remain at risk for PFAS because they were too young at age 5 years to engage in the battery of neuropsychological assessments required to confirm or rule out severe brain dysfunction. The risk of FAS/PFAS facial phenotypes (Ranks 3 to 4) was significantly increased among both women with average alcohol intake of 1 to 4 drinks/wk and women with isolated episodes of binge drinking, particularly during gestational weeks 3 to 4. These findings suggest that low-to-moderate levels of prenatal alcohol exposure or isolated binge exposures may place some fetuses at risk for FAS, PFAS, or other FASDs. Thus, conservative advice is still for women to abstain from alcohol consumption during pregnancy.

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CONFLICT OF INTEREST

None.

ETHICS

The LDPS was approved by the DNBC Board of Directors, the DNBC Steering Committee, the Regional Ethics Committee, the Danish Data Protection Agency, and the Institutional Review Board at the Centers for Disease Control and Prevention. Signed informed consent was obtained for the LDPS. The current analyses were approved by the DNBC Steering Committee and the Danish Data Protection Agency.

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APPENDIX • DETAILED PROCEDURES FOR TAKING AND SELECTING PHOTOGRAPHS FOR FACIAL CODING:

To examine the association between facial features used to diagnose FAS/PFAS and low-to-moderate prenatal alcohol exposure, digital photographs were obtained, selected, and categorized for FAS/PFAS criteria according to the FASD 4-Digit Code (Astley, 2004). Details of these procedures are described in this appendix.

Taking Digital Photographs

Each participant had a standardized frontal, oblique, and lateral digital facial photograph taken in accordance with the FAS Facial Photographic Analysis Software instructions (Astley, 2016). Briefly, the child had a relaxed facial expression (no smile, lips gently closed, eyes fully open with no eyeglasses), and the digital images had proper rotation, exposure, and focus. A 19.05-mm-diameter round paper sticker was placed between the participant's eyebrows as an internal measure of scale. Photographs were taken according to the protocol outlined in Astley (2016), and lead psychologists received in-person training on how to take the photographs by SA.

Selection of Photographs for Facial Coding

Resources and photograph quality did not permit the complete analysis of all 1,628 participants' photographs. Thus, a stepwise approach was used to identify those children with clear or suggestive indication of facial dysmorphia for further measurement. The goal was to identify all individuals that presented with 1, 2, or all 3 of the FAS facial features as defined above. The photographs were measured by authors AG and SA in a 2-step process, masked to the participant's alcohol exposure.

- Step 1: AG measured the PFLs and lip circularities of all 1,628 participants regardless of the quality of the feature in the photograph (e.g., the eyes were not fully open, the child was smiling, or the sticker curled). If the eyes are not fully open, the child is smiling, or the sticker is slightly curled, the direction of error will always be in 1 direction; the PFLs will be shorter, the lip thinner, and the philtrum smoother than they truly are. SA reviewed the subset from Step 1 that appeared to have short PFLs ≤ -1.5 SDs and/or thin upper lips (lip circularities ≥ 70) and identified the subset that had sufficient image quality to ensure the PFL and lip circularity measures could be accurately measured. SA then remeasured the PFLs and lip circularities of this subset to ensure the highest level of consistency and accuracy across all facial measures.
- Step 2: SA also reviewed the philtrum of all 1,628 participants and ranked only the subset with philtrum images of sufficient image quality and met criteria for Rank 4 or 5.

Final FAS/PFAS Determination

For all viable photographs, whenever a participant was identified as having at least 1 facial feature in the FAS range, the other 2 facial features were also measured if the quality of the image was sufficient. Once measurement of the 3 facial features was complete, the software generated a 4-Digit Code Facial ABC-Score and Face Rank (Fig. 1). For example, if a child presented with PFLs 2.6 SDs below the mean, a Rank 3 philtrum, and a Rank 2 upper lip, they would receive a Facial ABC-Score of CBA and a Face Rank of 2 (mild). If 1 or 2 of the 3 facial features could not be measured, an "X" was placed in the ABC-Score to signify its absence (e.g., the ABC-Score XCA signifies that the PFL could not be measured, but the philtrum was a "C" and the lip was an "A" [see Fig. 1*B*]). A Face Rank could not be generated if 1 or 2 of the 3 features could not be measured, but Facial ABC-Scores with 1 or 2 missing features could be used to accurately rule out 1 or more of Face Ranks 1 to 4. For example, if a Facial ABC-Score was XXA, Face Ranks 3 and 4 can be accurately ruled out despite not knowing the outcome of the PFL or philtrum, because neither can include a feature with a Rank A.

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Global DNA Methylation and Histone Posttranslational Modifications in Human and Nonhuman Primate Brain in Association with Prenatal Alcohol Exposure

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Background: Based upon experimental animal studies, the neurodevelopmental abnormalities associated with prenatal alcohol exposure (PNAE)/fetal alcohol spectrum disorder (FASD) have been attributed, at least in part, to epigenetic modifications. However, there are no direct analyses of human brain tissue.

Methods: Immunohistochemical detection of global epigenetic markers was performed on temporal lobe samples of autopsied fetuses and infants with documented PNAE. They were compared to age-, sex-, and postmortem delay-matched control cases (18 pairs; 20 to 70.5 weeks postconception). Temporal lobe tissue from a macaque monkey model of PNAE was also studied (5.7 to 6 months of age). We used antibodies targeting 4 DNA cytosine, 4 histone methylation, and 6 histone acetylation modifications and assigned scores based upon the semiquantitatively graded intensity and proportion of positively labeled nuclei in the ventricular and subventricular zones, ependyma, temporal cortex, temporal white matter, dentate gyrus (DG), and CA1 pyramidal layer.

Results: Temporal changes were identified for almost all marks according to the state of maturation in the human brain. In the DG (and 3 other brain regions), a statistically significant increase in H3K9ac was associated with PNAE. Statistically significant decreases were seen among 5mC, H3K4me3, H3K9ac, H3K27ac, H4K12ac, and H4K16ac in select regions. In the macaques, H3K36me3 decreased in the DG, and the ependyma showed decreases in 5fC and H3K36me3.

Conclusions: In human brain, global intranuclear epigenetic modifications are brain region and maturation state-specific. These exploratory results support the general hypothesis that PNAE is associated with a global decrease in DNA methylation, a global decrease in histone methylation, and a global increase in histone acetylation. Although the human and monkey subjects are not directly comparable in terms of brain maturation, considering the rapid temporal changes in global epigenetic modifications during brain development, interspecies comparisons may be extremely difficult.

Key Words: Acetylation, Methylation, Epigenetics, Human Brain, Prenatal Alcohol.

AN ESTIMATED 10 to 15% of women in North America consume alcohol (ethanol) during pregnancy (Popova et al., 2017). Prenatal alcohol exposure (PNAE) is associated with spontaneous abortion, sudden unexplained death of an infant (SUDI), and fetal alcohol spectrum disorder (FASD). Individuals with FASD demonstrate neurodevelopmental malformations, cognitive deficits, and social and behavioral problems (Carson et al., 2010; Reynolds et al., 2011). The global prevalence of FASD is estimated to be 7.7 per 1,000 people (Lange et al., 2017), and it is considered one of the most common causes of neurodevelopmental abnormalities (Popova et al., 2012).

In individuals diagnosed with FASD, neuroimaging studies (MRI) have demonstrated a wide range of brain

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abnormalities including micrencephaly, abnormal gyral patterns, corpus callosum abnormalities, cortical thinning, and reductions in regional brain volume (e.g., basal ganglia, diencephalon, and cerebellum; Donald et al., 2015; Jacobson et al., 2017; Moore et al., 2014; Nardelli et al., 2011; Norman et al., 2009). In our recent descriptive study of 174 human autopsy cases (fetuses, infants, children, teens, and adults) with PNAE or FASD, we identified 31 cases with micrencephaly, 6 cases with simple hydrocephalus, 6 with corpus callosum defects, 5 with neural tube defects, 5 with prenatal ischemic lesions, and 4 cases with heterotopias (Jarmasz et al., 2017).

The pathogenesis of PNAE/FASD-associated brain anomalies is not well understood. Many molecular studies in animals suggest that epigenetic modifications are involved (Chater-Diehl et al., 2017; Lussier et al., 2017). Epigenetics includes a range of acquired and inheritable chemical modifications found within and surrounding (i.e., histones) the genome that influences gene expression without direct changes to the nucleotide sequence of DNA (Feinberg, 2018). Epigenetics plays a substantial role in DNA replication and transcription, genomic imprinting, cellular differentiation, and cell death. Epigenetic processes include chromatin remodeling, RNA interference (micro RNAs), and covalent reversible chemical modifications to DNA (DNA cytosine modifications) or to histones (posttranslational modifications—PTMs; Feinberg, 2018). Recent reviews have summarized the epigenetic effects, mainly DNA methylation and histone posttranslational modifications (PTMs), in the brains of rodents exposed to alcohol in the pre- and postnatal (human third trimester equivalent) periods (Chater-Diehl et al., 2017; Laufer et al., 2017; Lussier et al., 2017). For a summary of PNAE epigenetic studies that studied the brain specifically, see Appendix S1.

Within the central nervous system, differentiation of neural stem/precursor cells into neurons, astrocytes, and oligodendrocytes is epigenetically driven (Coskun et al., 2012; Hirabayashi and Gotoh, 2010; Liu et al., 2016). For example, neural genes are activated through histone acetylation, whereas pluripotent genes and nonneural genes are repressed through histone methylation and DNA methylation (Hirabayashi and Gotoh, 2010).

To the best of our knowledge, PNAE-associated epigenetic changes have not been directly assessed in human brain tissue. In this study, temporal lobe and hippocampus samples from 18 prenatal alcohol-exposed fetuses and infants who had undergone autopsy (Jarmasz et al., 2017) were compared to age-matched controls using immunohistochemical detection of 4 DNA cytosine modifications, 4 histone methylation modifications, and 6 histone acetylation modifications. In parallel, we studied the temporal lobes from macaque monkey infants that had been exposed in utero to alcohol (Clarren et al., 1987, 1990). We hypothesized that PNAE is associated with global epigenetic changes that persist postnatally in the nuclei of brain cells.

MATERIALS AND METHODS

Human Autopsy Cases

Ethics approval was obtained from the University of Manitoba Research Ethics Board (#HS1311 – H2011:213). Details of the full PNAE/FASD autopsy cohort (N = 174) were described previously (Jarmasz et al., 2017). Because our hypothesis concerns epigenetic changes associated with PNAE, and because epigenetic changes can occur during postnatal life (Kundakovic and Champagne, 2015), we restricted our study to fetuses and infants <1 year. Exclusion criteria were as follows: documented in utero alcohol consumption by the mother in the clinical history of the autopsy report (see Jarmasz et al., 2017; for more details), no availability of formalin-fixed paraffin-embedded (FFPE) brain sample(s), extensive autolysis of brain tissue, severe hypoxic damage, cases dated <1988 (inconsistent FFPE), known gene mutations or chromosomal abnormalities, major brain malformations, bacterial meningitis, and a postmortem delay (PMD) > 48 hours. In our recent study, a PMD of >48 to 72 hours in pig and mouse brain tissue had adverse effects on histone acetylation marks (Jarmasz et al., 2019). When these histone acetylation marks were tested in a human brain microarray containing brain samples with PMDs of 96 and 120 hours, stability was >96 hours (Jarmasz et al., 2019). Age- and sex-matched controls were selected from the same autopsy database. Sex matching is important because there are documented differences in brain size, neurological disease prevalence, epigenetics, and stress response (Dekaban, 1978; Kigar and Auger, 2013; Menger et al., 2010; Shen et al., 2015). Inclusion criteria for age- and sex-matched controls were as follows: The case year had to be accrued within 10 years of the PNAE case, suffered little to no brain trauma, had no brain abnormalities, had no clinical history of prenatal alcohol or drug exposure, and had a PMD of ≤48 hours. A recent fetal case not described in the previous publication (Jarmasz et al., 2017) was included because the documented PNAE exposure was high despite not meeting the ≤48-hours PMD inclusion criteria. The PNAE cohort consisted of 9 fetuses or premature births with gestational age < 42 weeks and 9 infants age 43 to 70.5 weeks PC, along with controls. PNAE cohort epidemiologic and pathologic details are described in Table 1. PNAE and control pairings are described in Table 2. FFPE medial temporal lobe blocks stored at the pathology department (Health Sciences Centre, MB) were cut by microtome (5 to 6 μm thick) and mounted onto charged slides for immunohistochemistry.

Nonhuman Primate PNAE Brains

The *Macaca nemestrina* PNAE study was conducted in the 1980s (Bonthius et al., 1996; Clarren et al., 1987, 1988, 1990; Sheller et al., 1988), in compliance with University of Washington Administrative Policy for the humane treatment of animals used in research. Briefly, 48 pregnant adult female pig-tailed macaques received once-weekly nasogastric doses of ethanol ranging from 0.3 to 4.1 g/kg bodyweight; the highest dose is roughly equivalent to 16 standard distilled liquor drinks in a human (i.e., a binge exposure). High doses (2.5, 3.3, and 4.1 g/kg weekly) of alcohol were started at 33 to 46 days of gestation, rather than the time of fertilization, to reduce the risk of spontaneous abortion (Clarren et al., 1987). Controls received isocaloric sucrose. Thirty-three viable infants were born and subsequently assessed for overall health and features of the fetal alcohol syndrome phenotype (Clarren et al., 1988). The monkeys were killed at 5.7 to 7.2 months of age (Clarren et al., 1990), which is the human brain development equivalent of 2.7 to 3.5 years of age (http://translatingtime.org/translate). The cerebral hemispheres were bisected along the midsagittal plane and further dissected to produce multiple brain regions of interest for various studies. The right hemisphere was placed in 10% neutral buffered formalin for neuropathological study. After fixation (duration not documented),

Table 1. Clinical Details of Fetuses and Infants with Prenatal Alcohol Exposure

Case no.	Sex	Age	Cause of death	Brain weight (percentile)[a]	PNAE	Physical anomalies	Cardiac defects	Brain abnormalities
1	F	20 weeks' gestation	Stillborn/intrauterine death	≥10th to <50th	Alcohol abuse	–	–	None
2	F	21.5 weeks' gestation	Stillborn/intrauterine death	<5th	Rubbing alcohol 2nd trimester	None	None	Micrencephaly
3	M	27 weeks' gestation	Stillborn/intrauterine death	≥10th to <50th	Alcohol abuse	Facial anomalies, low-set ears, bilateral neck webbing	None	None
4	F	29 weeks' gestation	Stillborn/intrauterine death	Not indicated	Alcohol abuse	Low-set ears	None	None
5	M	34 weeks' gestation	Stillborn/intrauterine death	≥5th to <10th	Drank until pregnancy was determined	Low-set ears, palmar creases unusual	None	Micrencephaly
6	F	34 weeks' gestation	Intrapartum death with prematurity	<5th	Drank heavily throughout pregnancy	Facial anomalies, bilateral club foot and partial webbing of toes	Absent superior vena cava, large ASD	Micrencephaly, ventricle wall fusion (partial), periventricular heterotopia (rare), retarded laminar development cerebral cortex and hippocampus, hypoplasia pons
7	M	36 weeks' gestation	Stillborn/intrauterine death	≥10th to <50th	Occasional alcohol during the first trimester	None	Right coronary ostium	None
8	F	40 weeks' gestation	Stillborn/intrauterine death with placental abnormalities	<5th	Drank heavily during the third trimester	None	None	Micrencephaly
9	M	41 weeks' gestation	Stillborn/intrauterine death	<5th	History of alcohol abuse	None	None	Micrencephaly
10	M	21 days (43 weeks PC)	Bacterial + viral infection	<5th	Drank throughout pregnancy	None	None	Micrencephaly
11	F	23 days (43.5 weeks PC)	SUDI with unsafe sleeping environment	≥5th to <10th	Drank throughout pregnancy	None	None	Micrencephaly
12	M	6 weeks (46 weeks PC)	SUDI with congenital anomalies	≥10th to <50th	Drank during pregnancy (known alcoholic)	Thin upper lip	ASD with PDA	Recent mild hypoxic neuron change.
13	F	8 weeks (48 weeks PC)	SUDI with congenital anomalies	Not Indicated	Drank heavily during pregnancy	None	Small VSD	None
14	M	2 months (48.5 weeks PC)	SUDI with unsafe sleeping environment	≥10th to <50th	Drank during pregnancy	Low-set ears	Subaortic VSD	None
15	M	3 months (53 weeks PC)	SUDI	≥10th to <50th	Binged during pregnancy	None	None	None
16	F	4 months (57.5 weeks PC)	SUDI	≥10th to <50th	Drank during the first and second trimester	None	None	Periventricular leukomalacia, subacute (small foci in parietal white matter)
17	F	6 months (66 weeks PC)	SUDI	≥50th to <90th	Fetal alcohol syndrome	None	None	Polygyria
18	M	7 months (70.5 weeks PC)	SUDI	>95th	Mother alcoholic	Facial anomalies	None	None

PC, postconception; SUDI, sudden unexpected death of an infant.

[a]According to Maroun et al., 2005 *Pediatric and Developmental Pathology : The Official Journal of the Society for Pediatric Pathology and the Paediatric Pathology Society*. 8(2);204–17 and Phillips et al., 2009 *Pathology*. 41(6);515–26.

Table 2. Alcohol-Exposed Human Fetuses and Infants with Paired Control Cases

		Prenatal alcohol exposed			Age-, Sex-, and PMD-matched controls		
Case no.	Sex	PMD (hours)	Age (PC weeks)	Cause of death	PMD (hours)	Age (PC weeks)	Cause of death
1	F	24	20 weeks	Stillborn/intrauterine death	<24	21 weeks	Stillborn/intrauterine death with placental abnormalities
2	F	24.5	21.5 weeks	Stillborn/intrauterine death	21.5	22 weeks[a]	Intrapartum death: prematurity
3	M	7 to 8.5	27 weeks	Stillborn/intrauterine death	22	25 weeks	Stillborn/intrauterine death with placental abnormalities
4	F	49	29 weeks	Stillborn/intrauterine death	~24	31 weeks	Stillborn/intrauterine death with placental abnormalities
5	M	~24	34 weeks	Stillborn/intrauterine death with malformation(s)	56.5	33 weeks	Prematurity with pulmonary hypoplasia
6	F	107	34 weeks[a]	Intrapartum death: prematurity and malformation(s)	48	34 weeks[a]	Intrapartum death: prematurity and malformation(s)
7	M	48	36 weeks	Stillborn/intrauterine death	~1 to 5	37.5 weeks	Stillborn/intrauterine death
8	F	33	40 weeks	Stillborn/intrauterine death with placental abnormalities	32	38 weeks	Stillborn/intrauterine death
9	M	39	41 weeks	Stillborn/intrauterine death	~39 to 49	40 weeks	Stillborn/intrauterine death
10	M	28	43 weeks	Bacterial/viral infection	24 to 30	43 weeks	SUDI due to unsafe sleeping environment
11	F	20	43.5 weeks	SUDI due to unsafe sleeping environment	49	44 weeks	Asphyxiation due to accidental smothering
12	M	21	46 weeks	Malformations/congenital anomalies	26	46 weeks	SUDI due to unsafe sleeping environment
13	F	12	48 weeks	Malformations/congenital anomalies	24	48 weeks	SUDI
14	M	25 to 35	48.5 weeks	SUDI due to unsafe sleeping environment	47 to 53	48.5 weeks	SUDI due to unsafe sleeping environment
15	M	26	53 weeks	SUDI	36	53 weeks	SUDI
16	F	3.5 to 7.5	57.5 weeks	SUDI	~24	57.5 weeks	SUDI
17	F	8	66 weeks	SUDI	24 to 36	64 weeks	SUDI due to unsafe sleeping environment
18	M	19.5	70.5 weeks	SUDI	32 to 34	70.5 weeks	Accidental positional asphyxiation

F, Female; M, Male, PC, Postconception; PMD, Postmortem delay; SUDI, Sudden unexplained death of an infant.
[a]Liveborn; died within minutes to hours of birth.

the hemisphere was divided into 5 mm coronal slices and embedded in paraffin (Clarren et al., 1990). Blocks of FFPE tissue, which had been archived at the University of Washington, were transferred to the senior author's (MRD) laboratory. The available samples consisted of 6 to 8 coronal slices of 1 cerebral hemisphere extending from the occipital lobe tip to the frontal lobe at the level of the posterior striatum. In all cases, at least 1 slice included temporal lobe, hippocampus, thalamus, and posterior putamen. Because the paraffin was brittle, tissue blocks of interest were heated at 60°C for 30 minutes and reembedded in new paraffin. We used only the 3 highest PNAE levels (2.5, 3.3, and 4.1 g/kg; $N = 6$) along with controls (sucrose exposure only; $N = 5$; Appendix S2).

Antibodies to Epigenetic Modifications

We selected antibodies that detect epigenetic modifications known to occur in the brain, and/or have been reported to be affected by alcohol exposure in the prenatal, postnatal immature, or adult periods in either human brain cell lines or rodent brains (Chater-Diehl et al., 2017; Laufer et al., 2017; Lussier et al., 2017). These include 5-methylcytosine (5mC), 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC), 5-carboxycytosine (5caC), histone trimethylated at lysine 4 (H3K4me3), H3K9me2/K9me3, H3K27me3, H3K36me3, histone acetylated at lysine 9 (H3K9ac), H3K14ac, H3K27ac, H4K5ac, H4K12ac, and H4K16ac. We also included antibodies targeting total histone H3 and H4, as well as pan-acetyl H3 and H4. Rationale for inclusion of DNA/histone modifications in this study and technical details of the epigenetic antibodies are presented in Appendix S3 and Table 3. Antibody specificity and epitope tolerance to postmortem degradation is described in detail in a recent publication (Jarmasz et al., 2019).

Immunohistochemistry

Human and macaque brain tissue sections (5 to 6 μm thickness) were subjected to immunohistochemistry, which is described in detail in a recent publication (Jarmasz et al., 2019). Optimal primary antibody concentration was determined by running a series of dilutions greater and less than the manufacturers' suggestions (Appendix S4). Briefly, paraffin was melted at ~60°C, and tissue samples were rehydrated through multiple xylenes and graded ethanol solutions (100, 90, and 75%). Slides were subjected to antigen retrieval, as well as endogenous peroxidase blocked before incubation with 10% serum. The primary antibody was applied, followed by application of the secondary antibody, followed by application of peroxidase-conjugated streptavidin (with multiple 4-minute washes in-between each application). DAB (3,3′ diaminobenzidine) chromogen was used to develop the slides. The slides were counterstained with Harris hematoxylin solution, dehydrated through graded ethanol and multiple xylene solutions, coverslipped with Permount, and left to air-dry overnight.

Imaging of Immunohistochemical Results

Human and macaque slides were imaged using a standard upright microscope with digital camera (Olympus BX51TRF microscope, Olympus Scientific Solutions, Waltham, MA; Qimaging 32-0110A-568 MicroPublisher 5.0, Model LH100HG, Teledyne

Table 3. Details and Sources for the Antibodies to Epigenetic Marks

Antibody	Immunogen/target	Isotype	Species	Type	Company details	Lot no.
5mC	Recognizes 5-methylcytidine in vertebrate DNA	IgG	Mouse	Monoclonal (clone 33D3)	Active Motif, #39649	24516019
5hmC	Raised against 5-hydroxymethylcytosine conjugated to KLH	Serum	Rabbit	Polyclonal	Active Motif, #39769	06116002
5fC	Raised against 5-formylcytidine conjugated to KLH	Serum	Rabbit	Polyclonal	Active Motif, #61223	34711001
5caC	Raised against 5-carboxycytosine conjugated to KLH	Serum	Rabbit	Polyclonal	Active Motif, #61225	32115002
H3K4me3	Raised against a peptide including trimethyl-lysine 4 of histone H3.	Serum	Rabbit	Polyclonal	Active Motif, #39159	12613005
H3K9ac	Synthetic peptide corresponding to Human Histone H3 aa 1-100 (N-terminal) (acetyl K9) conjugated to KLH	IgG	Rabbit	Polyclonal	Abcam, #ab10812	GR287797-1
H3K9me2, K9me3	Synthetic peptide within human histone H3 aa1-100 (tri methyl K9); exact sequence is proprietary	IgG1	Mouse	Monoclonal (clone 6F12-H4)	Abcam, #ab71604	GR117765-1
H3K14ac	Synthetic peptide within human histone H3 (acetyl K14); exact sequence is proprietary.	IgG	Rabbit	Monoclonal (clone EP964Y)	Abcam #ab52946	GR302893-8
H3K27ac	Synthetic peptide corresponding to human histone H3 aa 1-100 (acetyl K27) conjugated to KLH	IgG	Rabbit	Polyclonal	Abcam, #ab4729	GR288020-1
H3K27me3	Synthetic peptide within human histone H3 aa 1-100 (tri methyl K27) conjugated to KLH; exact sequence is proprietary	IgG	Mouse	Monoclonal (clone 6002)	Abcam, #ab6002	GR275911-7
H3K36me3	Synthetic peptide within human histone H3 aa 1-100 (tri methyl K36) conjugated to KLH; exact sequence is proprietary	IgG	Rabbit	Polyclonal	Abcam, #ab9050	GR3177961-1
H4K5ac	Synthetic peptide within human histone H4 aa 1-100 (N-terminal) (acetyl K5); exact sequence is proprietary	IgG	Rabbit	Monoclonal (clone EP1000Y)	Abcam, #ab51997	GR295999-7
H4K12ac	Synthetic peptide corresponding to human histone H4 aa 10-15 (acetyl K12)	IgG	Rabbit	Polyclonal	Abcam, #ab61238	GR325039-3
H4K16ac	Synthetic peptide corresponding to human histone H4 (acetyl K16); exact sequence is proprietary	IgG	Rabbit	Monoclonal (EPR1004)	Abcam, #ab109463	GR187780-8
H3panAc	Peptide including acetyl-lysines contained in the N-terminal tail of human histone H3	IgG	Rabbit	Polyclonal	Active Motif, #61637	28915002
Total H3	Peptide containing the N-terminus of histone H3.	IgG2b	Mouse	Monoclonal (clone MABIO3O1)	Active Motif, #39763	34614001 5217020
Total H4	Synthetic peptide containing human histone H4.	IgG2b	Mouse	Monoclonal (clone MABI0400	Active Motif, #61521	7715006

KLH, keyhole limpet hemocyanin.

Qimaging, Surrey BC, Canada). Images were captured at 40×, 200×, or 400× total magnification using QCapture software (v2.8.1, 2001 to 2005, Qimaging Corp., Teledyne Qimaging, Surrey BC, Canada). The dentate gyrus (DG), CA1 neurons of the hippocampal formation (CA1), ependymal cells along the floor of the temporal horn of the lateral ventricle, temporal neocortex (CX) in the parahippocampal gyrus, and temporal white matter (WM) were evaluated. In human fetuses 34 weeks and younger, the germinal region along the roof of the lateral ventricle, including the ventricular zone (VZ) and subventricular zones (SVZ), was also evaluated. Two previously validated (Jarmasz et al., 2019) semiquantitative scales were used to score the estimated proportion of immunoreactive nuclei (graded 0 to 4; corresponding to approximately 0, 25, 50, 75, and 100% positive) and the graded intensity of immunoreactivity in comparison with a standard image set (graded 0 to 3.5 in 0.5 steps; see Additional file 13, in Jarmasz et al., 2019). Morphologic features of nuclei were used as a surrogate for probable brain cell type. Cells with large round nuclei and prominent nucleoli were considered as probable neurons; cells with medium-sized round or irregular nuclei were considered probable astrocytes (in WM) or possible small neurons in cortex; cells with small round nuclei were considered probable oligodendrocytes; cells with small elongated and irregular nuclei were considered probable microglia; cells with small elongated smooth-contoured nuclei near a vascular lumen were considered endothelial; and cells wrapping vascular endothelia were considered to be smooth muscle. First, control cases were examined in order to establish a general developmental pattern of expression for the epigenetic marks. Second, matched pairs of control and PNAE cases were compared in all brain regions. Not all epigenetic marks were evaluated in every single case. For example, focal tissue damage or imperfections in the immunostaining would preclude proper evaluation. The immunoreactivity scores (proportion and intensity grades) for every brain region were recorded in a Microsoft Excel spreadsheet.

Statistical Analyses

The multiplied proportion and intensity scores were graphed as a function of age for each anatomical region and presented as bar graphs using Microsoft Excel (Y-axis = total multiplied rank, X-axis = postconception age in weeks). Third-order polynomial trendlines ($y = (m_3{*}x^3 + m_2{*}x^2 + m_1{*}x) + b$) were superimposed to the graphed values to depict the general pattern of developmental expression for each epigenetic mark. PNAE data curves were added

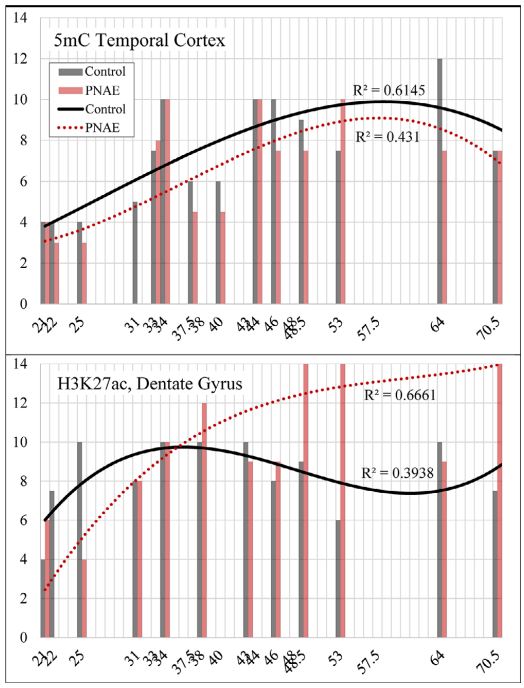

Fig. 1. Examples of human control and PNAE immunostaining scores with third-order polynomial curve fit with R^2 values. The gray bars and black solid curve represent controls, and the red bars and dotted curve represent PNAE cases. The *Y*-axis shows the semiquantitative scores, which is the product of intensity and distribution scores multiplied (maximum score of 14). The *X*-axis is the postconception age in weeks.

to highlight possible differences (Fig. 1). Goodness of fit (R^2) is shown on the graphs; the average R^2 value was 0.5352 ± 0.0246 (mean R^2 ± SEM) for controls and 0.5575 ± 0.0254 for PNAE. However, because the data represent 2 biologically different populations (i.e., stillborn fetuses with uncertain postmortem in utero conditions vs. liveborn infants) a formal polynomial regression fit to compare the curves is likely not valid. Data were subjected to multiple paired *t*-test (2-tailed) comparisons (JMP 14.1 statistical software; SAS Institute, Cary, NC) within 6 age clusters: 21 to 25 weeks PC (n = 3 pairs) and 31 to 34 weeks PC (n = 3 pairs) for the VZ and SVZ; 21 to 25 weeks PC (n = 3 pairs; early fetus), 31 to 40 weeks PC (n = 6 pairs; late fetus), 43 to 48.5 weeks PC (n = 5 pairs; young infant), and 53 to 70.5 weeks PC (n = 4 pairs; infants) for all remaining brain regions. As recommended for exploratory research, all p values are reported without correction for multiple tests (13 antibodies, 5 brain loci), acknowledging that p values marginally <0.05 should be interpreted with caution (Bender and Lange, 2001; Cipriani et al., 2015).

For the macaque brains, images were scored as described above. The Wilcoxon Rank Sums test with chi-square approximation (Kruskal–Wallis) was used to compare control and PNAE groups for each location and each antibody (JMP 14.1 statistical software; SAS Institute). The p values were manually adjusted using the Benjamini–Hochberg formula (Benjamini and Hochberg, 1995): $((i/m)*Q)$ and a false discovery rate (FDR) of 0.1. Those p values that did not remain significant after the Benjamini–Hochberg correction but were still below 0.05 are reported as trends.

RESULTS

General Observations Concerning Immunohistochemical Labeling of Histone Modifications

Most of the antibodies yielded strong and consistent immunolabeling in both human and monkey tissues. We had originally intended to study antibodies targeting total histone H3, total histone H4, pan-acetyl histone H3, pan-acetyl histone H4, H3K9me2, and H3K27me2. For total histone H3 and H4 antibodies, we expected the antibodies to label virtually every nucleus at all stages of maturation. Surprisingly, this was not the case (Appendix S5: Fig. 1). Similarly, we expected that histone H3 and H4 pan-acetyl antibodies would label more cells than any antibody targeting a single acetylated lysine. However, the proportion of cells labeled by anti-pan-acetyl histone H3 and H4 was much less than that labeled by single acetylation marks (Appendix S5: Fig. 1). Consequently, results of these are not reported. The H3K27me2 antibody binding was not blocked by the appropriate peptides. We were unable to get satisfactory cell labeling using the H3K9me2 antibody.

Developmental Expression of Epigenetic Modifications in Control Human Brain

Graphic representations of the human control and PNAE results are shown in Figs 2–6. Polynomial curves were fitted to the data for all location/epitope combinations; they provide a convenient way for visualizing and comparing the data sets.

Ventricular and Subventricular Zones

Developmental expression of epigenetic marks in the VZ varied considerably; 7/13 epigenetic marks (5mC, 5hmC, H3K36me3, H3K9ac, H3K14ac, and H4K5ac) exhibited a "U-" shaped expression curve prior to disappearance of the VZ at 31 to 34 weeks (Figs 2–5, 7; Appendix S5: Fig. 2). Note, however, that the sample sizes are small so we cannot be certain that the transient decline is real. In the SVZ, most marks started at low levels and increased with gestational age (5caC, H3K4me3, H3K36me3, H3K9ac, H4K5ac, and H4K12ac) (Figs 2–5; Appendix S5: Fig. 2). Within the SVZ, an anatomical gradient was evident for 5mC, H3K4me3, H3K36me3, H3K9ac, H3K14ac, H3K27ac, H4K5ac, H4K12ac, and H4K16ac; in the youngest fetuses, only the SVZ adjacent to the VZ was positive, followed by spreading to involve the entire SVZ prior to involution. Within the SVZ, there are different progenitor cell types (Rushing and Ihrie, 2016); however, they could not be easily distinguished due to similarity in size and morphology.

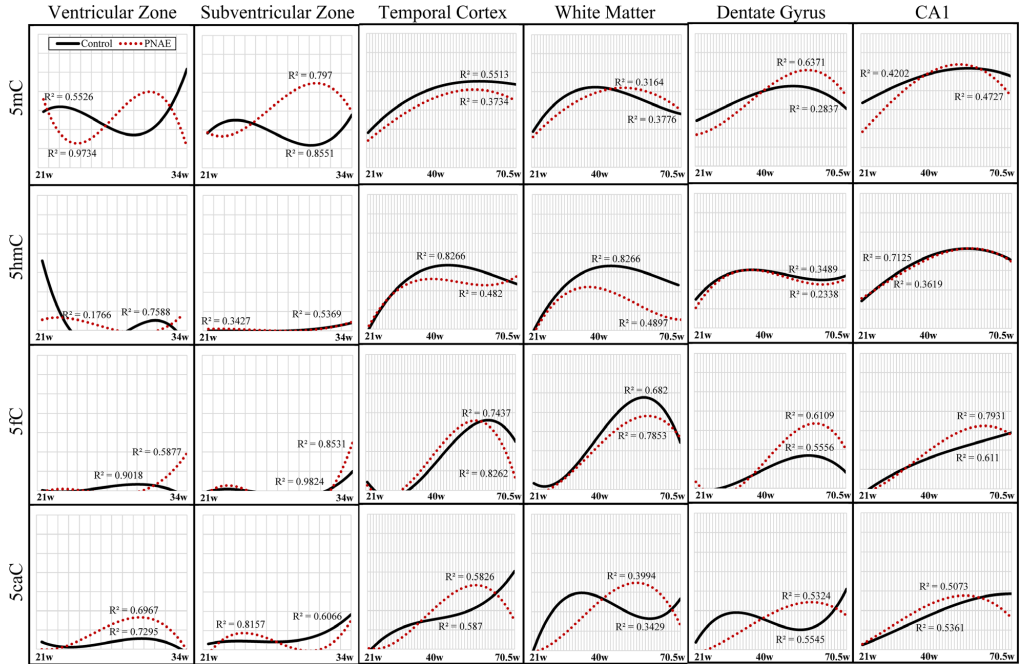

Fig. 2. Graphic representation of semiquantitative score values (maximum 14; *Y*-axis) for DNA cytosine modifications in the human brain regions assessed. The black curve represents the control cases, and the red dotted curve represents PNAE. Curve fit values (R^2) are also shown. The *X*-axis represents the postconception age in weeks. The ventricular (VZ) and subventricular zones (SVZ) are only present in fetal cases up to 34 weeks' gestation. In the VZ and SVZ, 5mC levels were highest, while 5hmC, 5fC, and 5caC levels were low. In the other brain regions, 5mC, 5hmC, and 5caC (white matter only) show a gradual increase, peaking at birth, followed by a plateau or decrease. Although the control and PNAE curves diverged in some circumstances, only 5mC in the CA1 sector of the early fetal PNAE group showed a statistically significant decrease ($p = 0.0198$).

Brain Surface and Temporal Neocortex

Most epigenetic mark antibodies strongly labeled a narrow band of cells along the external surface from the earliest age studied (21 weeks; Fig. 8). This likely represents the marginal zone progenitor layer (Costa et al., 2007). The exceptions were anti-5mC and anti-5hmC, which showed only faint immunoreactivity in this location. In increasing maturity in fetal brains, epigenetic marks expressed in the cortical mantle tended to progress to increasing depths from the surface. Brain cell types were distinguishable through morphology with increasing age. Within the 5th and 6th cortical layers, all but 4 epigenetic marks (5fC, 5caC, H3K14ac, and H4K16ac) demonstrated ~75 to 100% positive staining among large (presumably neuronal) and intermediate-sized nuclei. In WM, small round (presumably oligodendroglial) nuclei demonstrated low positive proportions (≤50%) in the fetuses. In the infant cases, all marks except H3K4me3, H3K27ac, and H4K12ac increased to include ~50 to 100% of the presumptive oligodendrocytes. Epigenetic mark immunoreactivity varied considerably in presumed microglial nuclei. Active transcription marks (H3K4me3, H3K36me3, H3K27ac, H4K5ac, and H4K12ac) were most strongly expressed. Vascular endothelial cells and arterial smooth muscle cells had a seemingly random mix of positive and negative cells for most marks; the exceptions were almost uniform negativity for 5mC, 5hmC, 5fC, 5caC, and H4K16ac (Appendix S5: Fig. 3). Almost every antibody labeled choroid plexus epithelial cell nuclei (Appendix S5: Fig. 3).

White Matter

In presumed oligodendrocytes (small round nuclei), most epigenetic marks were more widespread and more strongly immunoreactive in infants than in fetuses; exceptions were H3K27me3, H3K27ac, and H4K12ac, which decreased in infancy. Among larger irregular (presumed astroglial) nuclei, H4K5ac and H4K12ac were expressed in ~100% of cells at all ages examined. All other epigenetic marks were present in a minority (~0 to 50%) of cells during the fetal stages and increased to a ~50 to 100% in infancy. Among the few very large nuclei of presumed WM neurons, stable immunoreactivity was seen for all epigenetic marks except for 5fC, 5caC, H3K14ac, and H4K16ac, which were negligible in early fetuses (21 to 25 weeks PC) but attained positivity in infancy (53 to 70.5 weeks PC).

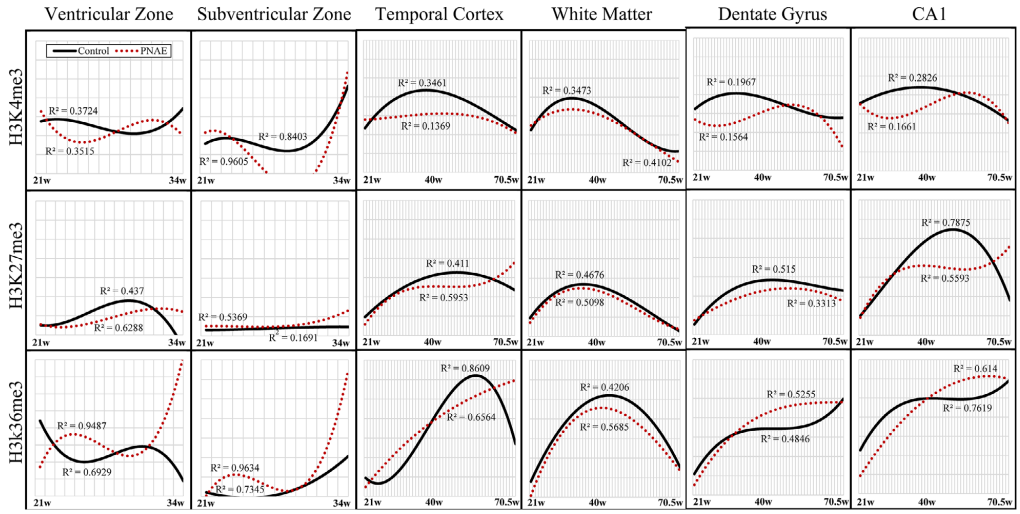

Fig. 3. Graphic representation of semiquantitative score values (maximum 14; *Y*-axis) for histone H3 methylation marks in the human brain regions assessed. The black curve represents the control cases, and the red dotted curve represents PNAE. Curve fit values (R^2) are also shown. In the control VZ, H3K4me3 was relatively stable while the other 2 declined with maturation. In the control SVZ, H3K27me3 was relatively stable while the other 2 increased with maturation. In all other brain regions, most of the marks showed a slight peak near birth. The exception was H3K36me3, which showed a steady increase in the DG and CA1 neurons. None of the histone methylation mark differences were statistically significant between PNAE and controls.

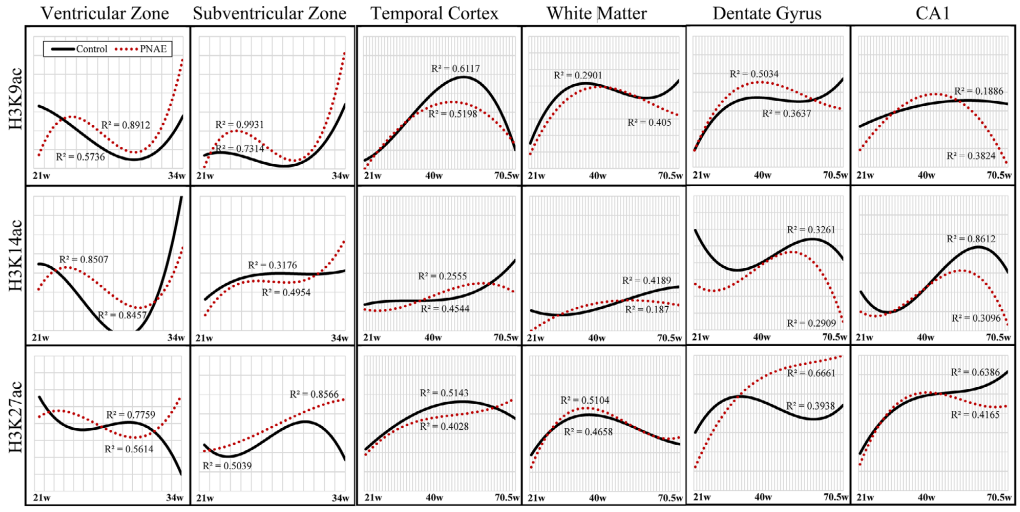

Fig. 4. Graphic representation of semiquantitative score values (maximum 14; *Y*-axis) for histone H3 acetylation marks in the human brain regions assessed. The black curve represents the control cases, and the red dotted curve represents PNAE. Curve fit values (R^2) are also shown. In the VZ and SVZ, H3K9ac and H3K14ac tended to increase with maturation while H3K27ac tended to decline. In the other brain regions, all of the marks tended to increase during the fetal period. Some differences were observed in association with PNAE. In the cortex, H3K9ac ($p = 0.0202$) and H3K27ac ($p = 0.0229$) were lower in young infants with PNAE. In the white matter, H3K9ac was lower ($p = 0.0377$) in the early fetal PNAE group compared with controls. In the dentate gyrus, H3K9ac was higher ($p = 0.0352$) in young PNAE infants. In the CA1, H3K27ac was lower ($p = 0.0414$) in PNAE infants.

Dentate Gyrus Neurons and Pyramidal Neurons of Hippocampal CA1 Region

In human fetuses, granular neurons of the DG were ~50 to 75% positive for all epigenetic marks except for H3K27ac and H4K5ac, which were ~100% positive; the latter 2 are marks of active transcription. Almost all epigenetics marks increased in infancy except for 5hmC, 5fC, H3K4me3, and H4K5ac, which remained consistent. The proportion of CA1

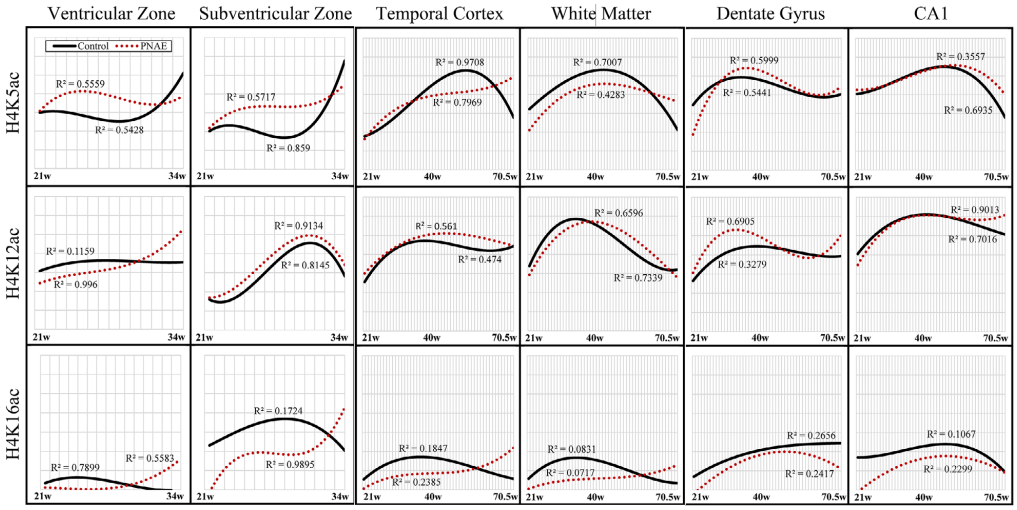

Fig. 5. Graphic representation of semiquantitative score values (maximum 14; *Y*-axis) for histone H4 acetylation marks in the human brain regions assessed. The black curve represents the control cases, and the red dotted curve represents PNAE. Curve fit values (R^2) are also shown. In the VZ and SVZ, H4K5ac tended to increase with maturation. In the other brain regions, most marks tended to increase during the fetal period and decrease during infancy. H4K16ac was significantly lower in the dentate gyrus ($p = 0.0339$) of young infants with PNAE.

pyramidal neurons immunoreactive for 5fC, 5caC, H3K14ac, and H4K16ac was low (~25 to 50%), while all other epigenetic marks were expressed in the majority of cells (~75 to 100%). Immunoreactivity for most epigenetic marks remained consistent from the fetal period to infancy. Exceptions were 5mC, 5fC, H3K4me3, H3K9ac, H3K14ac, and H4K16ac, which all increased (H4K16ac went from ~25% to ~100%).

Temporal Lobe Ependymal Cells

For most epigenetic marks, nuclei of the temporal horn ependymal cells started at ~25 to 50% positive in fetuses and increased to ~75% positive in infants.

Differential Expression of Epigenetic Marks Between Brain Cell Types (see Appendix S6)

In control and PNAE cases, all epigenetic marks except for 5fC, 5caC, H3K9ac, H3K14ac, and H4K16ac were identified in essentially all brain cell types. During the fetal period, almost all epigenetic marks were preferentially expressed in more mature cells that could be identified as neurons. 5hmC and H4K16ac appeared to be relatively specific to large hippocampal and cortical neurons. For 5mC, 5hmC, H3K27me3, H3K36me3, H3K9ac, and H4K16ac, the dentate neurons demonstrated a maturation gradient, where more mature nuclei distant from the germinal layer (i.e., distant from CA4 sector of the hippocampus) were positive, while less mature nuclei near the germinal layer were negative.

Comparison of Epigenetic Marks in Control and PNAE Brains

Statistical comparisons between human control and PNAE pairings are summarized in Table 4. In the young fetuses, the VZ of PNAE cases had less H4K16ac immunoreactivity than controls ($p = 0.0039$). The temporal cortex (a mix of neurons and glial cells) of young infant PNAE cases had less H3K9ac ($p = 0.0202$) and H3K27ac ($p = 0.0229$) immunoreactivity than controls (Fig. 9). For both marks, the difference was reflected in intensity for all cell types, and specifically a loss of immunoreactivity in small round nuclei (presumably oligodendrocytes) for H3K27ac (Fig. 9). H3K9ac showed less immunoreactivity in PNAE WM ($p = 0.0377$; Fig. 10) and among the ependyma cells of the young fetuses ($p = 0.0198$; Fig. 11). Ependymal cells also exhibited decreases in intensity for H3K4me3 ($p = 0.0234$) and a decrease in the number of positive nuclei for H3K27ac ($p = 0.0142$) in the early fetal age group (Fig. 11). In the DG neurons of young infants, an increased intensity was observed for H3K9ac ($p = 0.0352$) (Fig. 10), and a decreased intensity was seen for H4K16ac. In the CA1 neurons of PNAE cases, a smaller proportion were 5mC positive ($p = 0.0198$) and reduced immunoreactivity was seen for H3K27ac ($p = 0.0414$). Overall, H3K9ac exhibited a notable difference in 4 of the 7 brain regions studied and appeared to be the only epigenetic mark affected by PNAE in both the human fetal and infant groups (Figs 9–11).

In the macaque brains, there were few statistically significant differences between the control and PNAE samples (Table 5). In the DG neurons of the PNAE group,

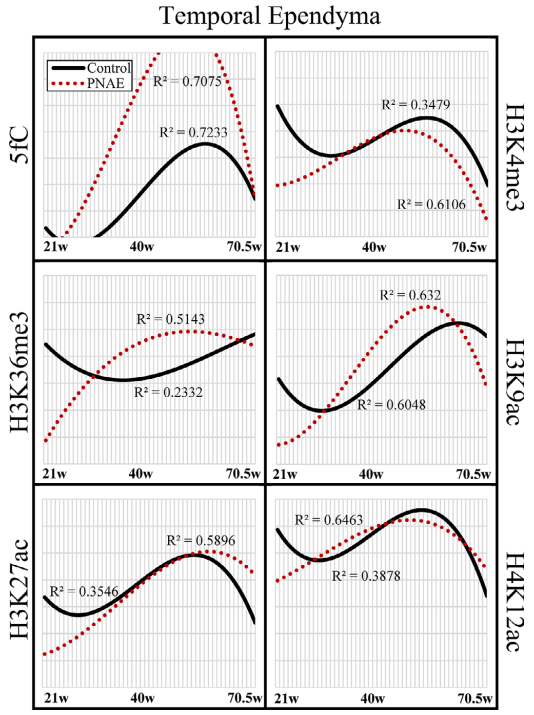

Fig. 6. Graphic representation of semiquantitative score values (maximum 14; *Y*-axis) in the human temporal ependyma. The black curve represents the control cases, and the red dotted curve represents PNAE. Curve fit values (R^2) are also shown. In the early fetal age group, H3K4me3 (p = 0.0234), H3K9ac (p = 0.0198), and H3K27ac (p = 0.0142) were all significantly lower in PNAE compared with controls.

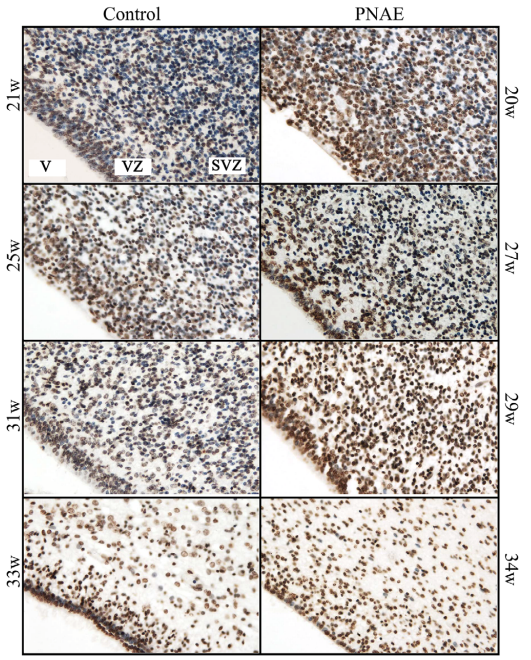

Fig. 7. Photomicrographs showing 5-methylcytosine (5mC) immunoreactivity in human ventricular (VZ) and subventricular zones (SVZ). In controls, most cells of the VZ are strongly positive until it is replaced by the ependymal layer at 31 to 34 weeks. Immunoreactivity in the SVZ increased slightly with fetal maturation. In PNAE cases, 5mC was slightly greater than in controls. Images were taken at 200× magnification. DAB detection of antibody (brown) with hematoxylin counterstain (blue). The postconception age in weeks (w) is indicated for each panel. V = ventricle.

H3K36me3 exhibited less immunoreactivity (p = 0.0054) (Fig. 12). Decreases were observed among the epigenetics marks 5fC (p = 0.0077) and H3K36me3 (p = 0.0058) in the temporal lobe ependyma (Appendix S7).

DISCUSSION

Epigenetic modifications play an important role in brain development, guiding the specification, differentiation, and maturation of neural progenitor cells (NPCs). NPCs in the mouse neural tube gain 5mC during specification, gain 5hmC during differentiation, and then lose 5mC in the later stages of maturation (Zhou, 2012). Similarly, in dentate granule neurons of the developing mouse hippocampus, a methylation gradient correlates with the outside-in pattern of neuronal maturation (Chen et al., 2013). Studies of rat and mouse brains have demonstrated associations between development and histone PTM changes (Cho et al., 2011; Hahn et al., 2013; Podobinska et al., 2017; Resendiz et al., 2014; Zhang et al., 2012). In order for stem cells to change from totipotency to pluripotency, active histone PTMs are present on gene promoters such as H3K27ac and H3K4me3. After NPCs begin to differentiate, many gene promoters are in a bivalent (poised state) with repressive histone PTMs such as H3K27me3 and activating histone PTMs such as H3K4me3 dually expressed, allowing them to rapidly turn on and off. When a brain cell is fully differentiated, repressive histone PTMs such as H3K27me3 are typically dominant (Podobinska et al., 2017). H3K4me2 and histone acetylation levels increase during differentiation of mouse NPCs (Resendiz et al., 2014; Zhang et al., 2012). Compared to NPCs, mature mouse cortical neurons are enriched in histone acetylation marks (Cho et al., 2011). Corresponding to findings in developing rodent brains, regulatory processes are reflected in our developmental expression graphs. For example, in hippocampal CA1 neurons, which can be identified without ambiguity, H3K27me3 (repressive) demonstrates a gradual increase during the fetal period (differentiation), followed by a gradual decrease during infancy. In contrast, H3K27ac (activating) demonstrated a gradual increase during infancy. These findings suggest that human hippocampal neurons have not reached genetic maturity in infancy, which is entirely consistent with observations that neuron size

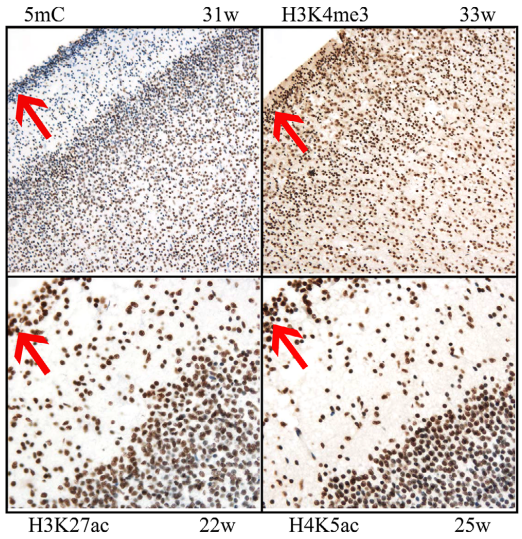

Fig. 8. Photomicrographs showing immunoreactivity for 4 epigenetic marks at the surface of temporal neocortex from normal human fetuses. The narrow band of immature marginal zone cells (red arrows) is positive for H3K4me3, H3K27ac, and H4K5ac, and negative for 5mC. Cells in deeper, more differentiated, layers of the cortex show mixed immunoreactivity. Images were taken at 20× (upper panels) and 200× (lower panels) magnifications. DAB detection of antibody (brown) with hematoxylin counterstain (blue). The gestational age in weeks (w) is indicated in each panel.

increases between 9 months and 16 years (Arnold and Trojanowski, 1996) and that synaptophysin accumulates in the CA1 sector throughout childhood and teenage years (Eastwood et al., 2006). However, because these immunohistochemical methods detect global (i.e., the average of 1,000s of gene loci) changes, we cannot infer specific functional changes with respect to any particular gene.

The VZ and SVZ, which collectively form the germinal matrix, in simplest terms give rise to glutamatergic and GABAergic interneurons, respectively (Adle-Biassette et al., 2018; ten Donkelaar, 2000). The SVZ also gives rise to precursors of astrocytes and oligodendrocytes. The size and proliferative activity within the SVZ peak between 20 and 26 weeks of gestation (Del Bigio, 2011), followed by rapid involution to 30 to 32 weeks and more gradual disappearance thereafter (Arshad et al., 2016). The proliferation peak in the temporal lobe is earlier (M. R. Del Bigio; unpublished findings). Our graphs of epigenetic PTMs suggest global increases in SVZ cell expression of H3K4me3, H3K9ac, and H4K5ac (which are all associated with active gene transcription) around the time of involution prior to 34 weeks gestation when the cells are leaving the proliferative stage. In the VZ of midgestation human fetuses studied here, PNAE was associated with reduced H4K12ac. However, in the SVZ no significant changes were observed. Ethanol has profound effects on the on survival and proliferation of NPCs (Boschen and Klintsova, 2017; Resendiz et al., 2014; Smith et al., 2014; Wilhelm and Guizzetti, 2016). This toxicity could account for the microcephaly in FASD (De La Monte and Kril, 2014; Jarmasz et al., 2017).

Among CA1 neurons of the fetal hippocampus, PNAE was associated with reduced immunoreactivity for 5mC, which is typically a gene transcription silencer. Within temporal cortex and hippocampus of young infants, we observed differential expression of several epigenetic marks in association with PNAE. The affected histone marks all play a role in active gene transcription. In experimental animals, most in utero and postnatal alcohol exposures caused a decrease in DNA methylation, a decrease in histone methylation, and an increase in histone acetylation (Chater-Diehl et al., 2017; Laufer et al., 2017; Lussier et al., 2017). These are in partial alignment with our results.

Because rodent brains are relatively immature at birth, many experiments use early postnatal alcohol administration to model late gestation human in utero exposure. Hippocampal and neocortical tissue from mice and rats that received alcohol during postnatal days 1 to 11 had increases in global DNA methylation, H3K4me3, H3K9me2, H3K27me2, and H3K27me3 (Chater-Diehl et al., 2016; Otero et al., 2012; Subbanna et al., 2013, 2014) and decreases in H3K9me2 and H3K27me2 (Subbanna et al., 2013). These results do not coincide with our findings. Discrepancies may be due to brain-specific interspecies differences or the absence of the maternal influences (i.e., maternal and placental metabolism) in the postnatal rodent experiments (Burd et al., 2007). In 1 recent study, mice were injected with ethanol (2.5 g/kg) on postnatal day 7 and euthanized ~8 h later. Global DNA methylation was decreased in the hippocampus and the cortex of ethanol-treated mice when compared to saline-treated mice (Nagre et al., 2015). This correlates with our findings in early fetuses despite the use of different methods. We must point out, however, that we do not know the interval between PNAE and fetal death.

In the absence of overt morphologic abnormalities, we observed several changes in epigenetic marks among the mature ciliated ependymal cells in both human and macaque PNAE. H3K4me3, H3K9ac, and H3K27ac were significantly reduced in humans, while 5fC and H3K36me3 were significantly reduced in macaques. The ependyma serves several functions including provision of a barrier between cerebrospinal fluid (CSF) and brain extracellular space, facilitating movement of signaling molecules in the CSF, and providing a niche for mature brain subventricular zone (stem) cells (Del Bigio, 2010; Ohata and Alvarez-Buylla, 2016). Little is known about epigenetic regulation in the mature ependymal layer. It is worth noting that, although none of the human cases studied here were hydrocephalic, hydrocephalus due to aqueduct stenosis was one of the more frequent malformations encountered in our PNAE/FASD autopsy study (Jarmasz et al., 2017). Integrity of the ependymal lining along the cerebral aqueduct is necessary for maintaining patency (Sival et al., 2011). We must consider the

Table 4. Statistically significant results for human control and PNAE pairings (n = 18 pairs)

	VZ		SVZ		Temporal cortex				White matter			
	21 to 25 PC weeks	31 to 34 PC weeks	21 to 25 PC weeks	31 to 34 PC weeks	Early fetus	Late fetus	Young infant	Infant	Early fetus	Late fetus	Young infant	Infant
5mC	↓ p = 0.4825	↓ p = 0.9195	↓ p = 0.2254	↑ p = 0.0955	↓ p = 0.1835	↓ p = 0.1939	↓ p = 0.0925	↓ p = 0.6156	↓ p = 0.1917	↓ p = 0.5932	↓ p = 0.4226	↑ p = 0.8020
5hmC	↓ p = 0.5616	↑ p = 0.4226	↑ p = 0.4226	n/a	↑ p = 0.3206	↓ p = 0.5492	↓ p = 0.1885	↓ p = 0.5736	↓ p = 0.4226	↑ p = 0.6509	– p = 1.0	↓ p = 0.4557
5fC	n/a	↑ p = 0.3103	n/a	↑ p = 0.5470	n/a	↑ p = 0.5367	↑ p = 0.6889	↓ p = 0.5903	↓ p = 0.5000	↓ p = 0.6810	↓ p = 0.6352	↓ p = 0.6560
5cac	↓ p = 0.7418	↑ p = 0.2254	↓ p = 0.8995	↓ p = 0.0942	↓ p = 0.5000	↓ p = 0.4950	↑ p = 0.6838	↓ p = 0.9296	↓ p = 0.5000	↓ p = 0.2754	↑ p = 0.4097	↓ p = 0.5000
H3K4me3	↓ p = 0.7479	– p = 1.0	↑ p = 0.8727	↓ p = 0.2601	↑ p = 0.8600	↓ p = 0.4702	*↓ p = 0.0714*	↓ p = 0.4226	↑ p = 0.8164	↓ p = 0.7595	↓ p = 0.5799	*↓ p = 0.0572*
H3K27me3	↓ p = 0.4226	↑ p = 0.4226	↑ p = 0.4226	↑ p = 0.1660	↓ p = 0.5286	↓ p = 0.7595	↓ p = 0.1086	↑ p = 0.8593	↓ p = 0.4226	↑ p = 0.8925	↓ p = 0.2495	n/a
H3K36me3	↓ p = 0.6815	↑ p = 0.1588	↑ p = 0.3206	↑ p = 0.1066	↑ p = 0.7060	↑ p = 0.5465	↓ p = 0.2044	↑ p = 0.7418	↓ p = 0.9388	↓ p = 0.8084	↓ p = 0.2149	↓ p = 0.2522
H3K9ac	↓ p = 0.5070	↑ p = 0.0955	↑ p = 0.6667	↑ p = 0.0942	*↓ p = 0.0572*	↑ p = 0.5401	↓ **p = 0.0202**	↓ p = 0.4226	↓ **p = 0.0377**	↓ p = 0.6350	↑ p = 0.9553	↓ p = 0.3832
H3K14ac	↓ p = 0.8379	↑ p = 0.4226	↓ p = 0.5509	↑ p = 0.2079	↓ p = 0.7952	↓ p = 0.5304	↑ p = 0.2412	↓ p = 0.5979	↓ p = 0.2578	↑ p = 0.5082	– p = 1.0	↓ p = 0.4778
H3K27ac	↓ p = 0.8520	↑ p = 0.2811	↑ p = 0.8845	↑ p = 0.0904	↓ p = 0.7240	↓ p = 0.7295	↓ **p = 0.0229**	↑ p = 0.7204	↓ p = 0.7852	↑ p = 0.4226	↓ p = 0.8528	↑ p = 0.5624
H4K5ac	↑ p = 0.1917	↓ p = 0.8845	↑ p = 0.4928	↑ p = 0.9139	↑ p = 0.7072	↑ p = 0.8240	↓ p = 0.1835	↑ p = 0.8556	↓ p = 0.4522	↓ p = 0.1836	– p = 1.0	↑ p = 0.9423
H4K12ac	↓ **p = 0.0039**	↑ p = 0.2567	↑ p = 0.6891	↑ p = 0.4380	↑ p = 0.1869	↑ p = 0.6971	↓ p = 0.7295	↑ p = 0.2254	↓ p = 0.6035	– p = 1.0	n/a	↑ p = 0.6657
H4K16ac	↓ p = 0.1994	↑ p = 0.1660	↓ p = 0.0815	↑ p = 0.8075	↓ p = 0.2222	↓ p = 0.4119	↓ p = 0.1529	↑ p = 0.3949	↓ p = 0.1835	*↓ p = 0.0661*	↓ p = 0.1359	↑ p = 0.6560

	Temporal ependyma				Dentate gyrus				CA1			
	Early fetus	Late fetus	Young infant	Infant	Early fetus	Late fetus	Young infant	Infant	Early fetus	Late fetus	Young infant	Infant
5mC	↓ p = 0.4326	↑ p = 0.7202	↓ p = 0.7209	↑ p = 0.6914	↓ p = 0.4226	↓ p = 0.8077	– p = 1.0	↑ p = 0.1917	↓ **p = 0.0198**	↓ p = 0.7717	↓ p = 0.4226	↓ p = 0.4226
5hmC	↑ p = 0.6667	↓ p = 0.4296	↓ p = 0.2601	↓ p = 0.7234	– p = 1.0	↓ p = 0.6349	↑ p = 0.8845	↓ p = 0.7779	↑ p = 0.2697	↓ p = 0.8399	↓ p = 0.4226	n/a
5fC	n/a	↑ p = 0.2413	↑ p = 0.0872	↑ p = 0.4208	n/a	↑ p = 0.3910	↓ p = 0.9649	↑ p = 0.2780	n/a	↑ p = 0.7090	↓ p = 0.9448	↑ p = 0.5529
5cac	↓ p = 0.5000	↑ p = 0.2941	↓ p = 0.8248	↓ p = 0.5000	↓ p = 0.5000	↓ p = 0.2444	↑ p = 0.4611	↓ p = 0.9097	↑ p = 0.5000	↑ p = 0.7045	↑ p = 0.4720	↓ p = 0.5000
H3K4me3	↓ **p = 0.0234**	↑ p = 0.1856	↓ p = 0.5112	↓ p = 0.3745	↓ p = 0.5228	↓ p = 0.6140	↓ p = 0.1675	↓ p = 0.5492	↓ p = 0.6278	↓ p = 0.6638	↓ p = 0.0797	↑ p = 0.6621
H3K27me3	↓ p = 0.7418	↑ p = 0.2620	↑ p = 0.9388	↓ p = 0.8725	– p = 1.0	↓ p = 0.7707	↓ p = 0.1849	↓ p = 0.2379	↓ p = 0.8740	↓ p = 0.8614	↓ p = 0.1835	↑ p = 0.8870
H3K36me3	↓ p = 0.1839	– p = 1.0	↑ p = 0.1835	↑ p = 0.4078	↓ p = 0.9261	↓ p = 0.9299	↑ p = 0.1835	↑ p = 0.1835	↓ p = 0.4226	↓ p = 0.4740	↓ p = 0.4226	↑ p = 0.2254
H3K9ac	↓ **p = 0.0198**	↑ p = 0.4194	↑ p = 0.2379	↑ p = 0.9521	↓ p = 0.9374	↑ p = 0.5913	↑ **p = 0.0352**	↓ p = 0.6695	↓ p = 0.3681	↑ p = 0.8854	↑ p = 0.4226	↓ p = 0.3719
H3K14ac	↓ p = 0.1638	↓ p = 0.8907	↓ p = 0.2589	↓ p = 0.0979	↓ p = 0.2952	↓ p = 0.6584	↓ p = 0.6613	↓ p = 0.4776	↓ p = 0.5000	↑ p = 0.8052	↓ p = 0.8259	↓ p = 0.2057
H3K27ac	↓ **p = 0.0142**	↓ p = 0.7234	↑ p = 0.7852	↑ p = 0.1994	↓ p = 0.3232	↑ p = 0.4226	↑ p = 0.4341	↑ p = 0.2324	↓ p = 0.7538	↑ p = 0.4226	↑ p = 0.8706	↓ **p = 0.0414**
H4K5ac	↓ p = 0.2999	↓ p = 0.5908	↓ p = 0.4226	↑ p = 0.2048	↓ p = 0.1096	↑ p = 0.2152	↓ p = 0.2999	↑ p = 0.5000	– p = 1.0	↑ p = 0.1817	↓ p = 0.5112	n/a
H4K12ac	↓ p = 0.1038	↑ p = 0.9087	↓ p = 0.4226	↑ p = 0.4226	↑ p = 0.6129	↑ p = 0.1826	↑ p = 0.4226	– p = 1.0	↓ p = 0.2044	n/a	n/a	↑ p = 0.4226
H4K16ac	↓ p = 0.4226	↑ p = 0.4766	↓ p = 0.1828	↓ p = 0.6392	↓ p = 0.4226	↑ p = 0.8628	↓ **p = 0.0339**	↓ p = 0.5000	↓ p = 0.1460	↓ p = 0.6702	↓ p = 0.4460	n/a

Early fetus = 21 to 25 weeks postconception (PC); late fetus = 31 to 40 weeks PC; early infant = 43 to 48.5 weeks PC; infant = 53 to 70.5 weeks PC.
Up and down arrows represent the direction of change; a dash represents no change.
n/a represents comparisons that had low ranked values and too few comparisons to generate a valid p value.
Two-tailed p values are significant at $p < 0.05$ and are in bold; 1-tailed p values significant at $p < 0.05$ showing a trend are italic and underlined.

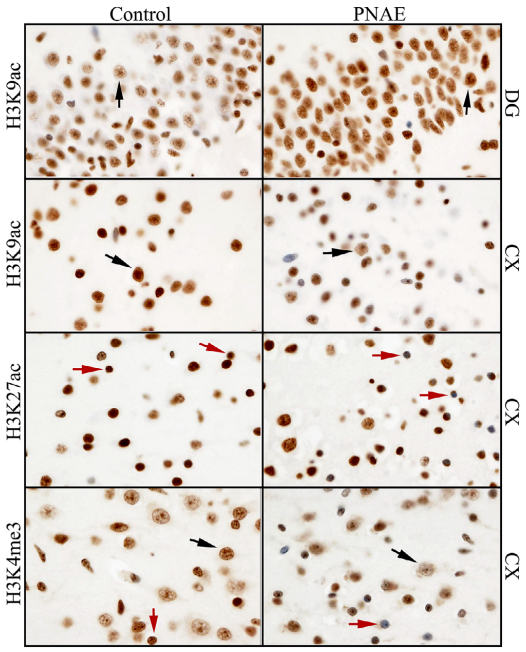

Fig. 9. Photomicrographs showing immunoreactivity for histone acetylation and methylation marks in human control and PNAE dentate gyrus (DG) and temporal neocortex. In the DG of young infants (43 weeks postconception), granular neurons of PNAE cases had greater immunoreactivity for H3K9ac than controls ($p = 0.0352$). In the temporal cortex of young infant PNAE cases, large neurons (black arrows) had less intense immunoreactivity than controls for histone marks H3K9ac ($p = 0.0202$) and H3K27ac ($p = 0.0229$). Reduced immunoreactivity was also apparent in small round nuclei (presumably oligodendrocytes; red arrows). Images were taken at 200× magnification. DAB detection of antibody (brown) with hematoxylin counterstain (blue).

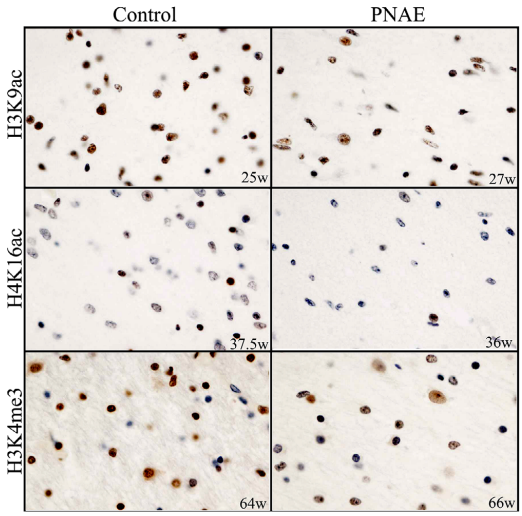

Fig. 10. Photomicrographs showing immunoreactivity for epigenetic marks in human control and PNAE white matter. Compared to controls, H3K9ac was lower in early fetal (21 to 25 weeks) PNAE ($p = 0.0377$). Both H4K16ac and H3K4me3 also tended to be lower ($p = 0.0661$ and $p = 0.0572$, respectively) in the late fetal (31 to 40 weeks) and infant (53 to 70.5 weeks) groups. These global decreases in immunoreactivity did not appear to be cell morphology specific. The postconception age in weeks (w) is indicated for each panel. Images were taken at 200× magnification. DAB detection of antibody (brown) with hematoxylin counterstain (blue).

possibility that PNAE-associated epigenetic changes might adversely affect the function of ependymal cells, which in turn could alter the health of the subjacent NPCs.

Owing to the difficulty obtaining human specimens with documented history of PNAE, there are numerous limitations to our study. (i) Small sample sizes in heterogenous groups are subject to type II errors (i.e., failure to identify real differences). (ii) We calculated numerous nonindependent paired t-tests, which increases the risk for type I error. Hence, these data must be considered exploratory and the reported p values should be viewed with caution. (iii) None of the cases had a comprehensive genetic (i.e., gene mutation) analysis, so we cannot be certain that abnormalities attributed to PNAE are, in fact, related to an unrecognized genetic disorder (Zarrei et al., 2018). We previously described many complex abnormalities and confounding factors in the autopsy cohort of PNAE/FASD cases (Jarmasz et al., 2017). Here, we avoided cases with severe malformations and attempted to restrict the analysis to brains of small size (micrencephaly). (iv) Hypoxic-ischemic stress frequently occurs prior to in utero death of fetuses; oxidative stress due to placental insufficiency could mask epigenetic changes caused by PNAE (Brocardo et al., 2011). In a largely overlapping cohort of human fetal and infant brains with a history of PNAE, we found immunohistochemical evidence for oxidative changes in the DNA and lipids of stillborn fetus brains, but there were no differences between controls and PNAE cases (Appendix S8). (v) We showed in a previous study (Jarmasz et al., 2019) that some histone acetylation marks diminish with increasing PMD. This necessitated the use of PMD time as an additional factor to be controlled, which in turn narrowed options for control cases. (vi) The unavoidably imprecise history of alcohol use (timing and quantity) during the pregnancy (Jarmasz et al., 2017) could explain the lack of consistent changes among epigenetic marks. Precisely timed studies in pregnant mice have shown, for example, that the offspring have different phenotypes when PNAE occurs on gestational day 7 compared with day 8 (Sulik, 2005). Extremely high doses at earlier stages can lead to more severe abnormalities such as neural tube defects (Hunter et al., 1994).

To compensate for the limitations of the human samples, we included a parallel analysis of macaque monkey binge PNAE brain samples. However, even within the controlled experiment, variable phenotypic outcomes were encountered (Clarren et al., 1990; Sheller et al., 1988). There are several possible reasons why our human and macaque results did

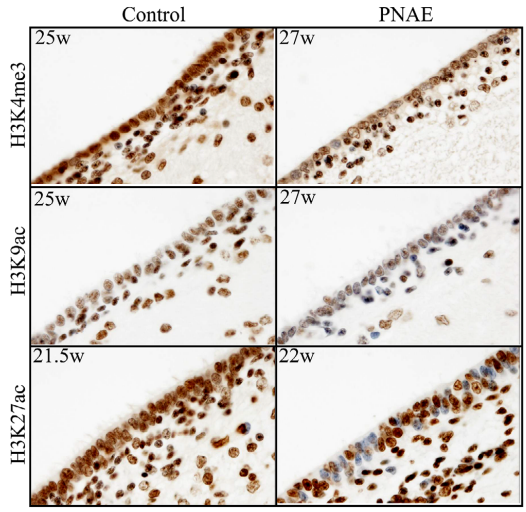

Fig. 11. Photomicrographs showing immunoreactivity for epigenetic marks in ependymal cells lining the temporal horn of human control and PNAE cases. Compared to controls, the intensities of H3K4me3 (p = 0.0234) and H3K9ac (p = 0.0198) were significantly lower in the early fetal age group (21 to 25 weeks). For H3K27ac, the proportion of positive cells was lower (p = 0.0142). The postconception age in weeks (w) is indicated for each panel. Images were taken at 200× magnification. DAB detection of antibody (brown) with hematoxylin counterstain (blue).

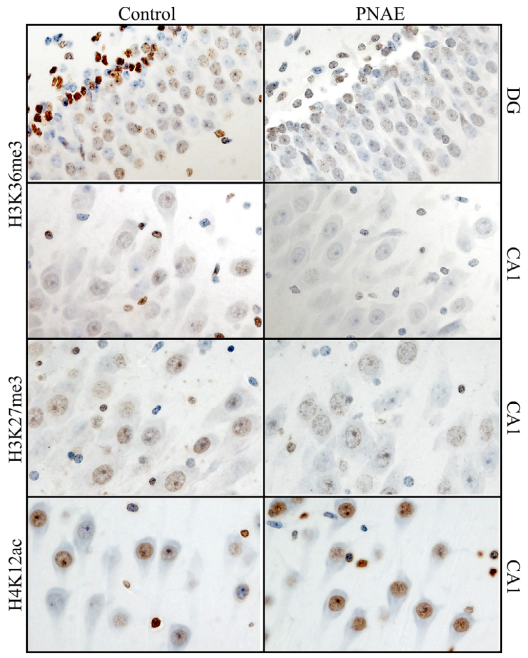

Fig. 12. Photomicrographs showing immunoreactivity for epigenetic marks in ~6-month-old control and PNAE macaque hippocampal neurons. H3K36me3 was significantly lower in the immature cells of the dentate gyrus adjacent to the cornu ammonis CA4 region (p = 0.0054). Among CA1 neurons, the proportions of neurons immunoreactive for H3K9ac (p = 0.0253) and H3K27me3 (p = 0.0146) were reduced in PNAE, while the proportion of H4K12ac-positive cells in PNAE cases was increased (p = 0.0445). Images were taken at 400× magnifications. DAB detection of antibody (brown) with hematoxylin counterstain (blue).

not correspond. The monkey brain sections required slightly different immunohistochemical techniques and often had inconsistent labeling, likely related to prolonged fixation in formalin. The humans died from natural causes, which would often include some degree of hypoxia, and the monkeys died from anesthetic overdoses, which are unlikely to immediately cause changes in epigenetics (Ju et al., 2016; Mori et al., 2014; Pekny et al., 2014). Although the monkeys survived a similar postnatal duration (6 months), in comparative developmental terms, they are approximately equivalent to 2.7- to 3.5-year-old humans (http://translatingtime.org/translate). In addition, a recent study documented transcriptional differences between the brains of humans and rhesus macaques in prenatal, early postnatal, and adult

Table 5. Statistically significant results for macaque control and PNAE pairings

Epigenetic mark	Ependyma	Temporal cortex	White matter	Dentate gyrus	CA1 neurons
5mC	↑ p = 0.8531	↓ p = 0.0821	↓ p = 0.5161	↑ p = 0.4601	↓ p = 0.7808
5hmC	↓ p = 0.1982	↓ p = 0.3367	↑ p = 0.3547	↓ p = 0.1570	↓ p = 0.0840
5fC	↓ **p = 0.0077**	↑ p = 0.5751	↓ p = 0.1961	↓ p = 0.3800	↓ p = 0.1024
5caC	↓ *p = 0.0210*	↑ p = 0.5080	↓ p = 0.1138	↓ p = 0.5192	– p = 1.0[a]
H3K4me3	↓ p = 0.5614	↓ p = 0.6435	↓ p = 0.4621	↑ p = 0.5541	↑ p = 0.6423
H3K9me2/K9me3	↓ p = 0.0910	p = 0.9004	↓ p = 0.7074	↑ p = 0.1898	↑ p = 0.7266
H3K27me3	↓ p = 0.1113	↓ p = 0.6873	↓ p = 0.3547	↓ p = 0.2667	↓ *p = 0.0146*
H3K36me3	↓ **p = 0.0058**	↓ *p = 0.0112*	↓ p = 0.1395	↓ **p = 0.0054**	↓ *p = 0.0253*
H3K9ac	↓ *p = 0.0427*	↓ p = 0.9228[a]	↓ p = 0.2278	↓ p = 0.9261	↓ p = 0.2733[a]
H3K27ac	↓ p = 0.3052	↓ p = 0.4388	↑ p = 0.3501	↑ p = 0.7010	↓ p = 0.8500
H4K5ac	↑ p = 0.3547	↑ p = 0.6620	↓ p = 0.5787	↑ p = 0.1303[a]	↑ p = 0.3613
H4K12ac	↓ p = 0.9247	↓ p = 0.1386	↑ p = 0.7813	↑ p = 0.9155	↑ *p = 0.0445*[a]

Bolded p values represent statistical significance at $p < 0.05$ after Benjamini–Hochberg correction at a false discovery rate of 0.1. p Values significant at $p < 0.05$ but failed Benjamini–Hochberg correction represent a trend and are italic and underlined.

↓—decreased in PNAE (n = 6) relative to control (n = 5); ↑—increased in PNAE (n = 6) relative to control (n = 5); "–" represents no change in PNAE (n = 6) relative to control (n = 5).

[a]Minimal immunoreactivity.

stages of life. The postconception day 60 macaque specimens were fairly closely aligned with postconception day 102 to 115 human samples, while 2- to 7-year-old macaques aligned with adolescent and adult human samples. This indicates a protracted development of the brain in humans in comparison with rhesus macaques at the level of gene transcription, which is an epigenetically driven process (Zhu et al., 2018).

A major target in FASD research is identification of a DNA methylation pattern sufficiently characteristic to be used as a biomarker for early diagnosis in living children. This usually relies on whole genome methylation analysis of DNA extracted from leukocytes or buccal epithelium cells. In buccal cells from 12 males with FASD (3 to 6 years), 269 differentially methylated cytosine–phosphate–guanines (CpGs) were identified (Laufer et al., 2015). In buccal cells from 110 FASD and 96 control children (5 to 18 years), differentially methylated CpGs were found in 403 genes, many of which are related to neurons and brain diseases (e.g., autism, epilepsy, substance abuse; Portales-Casamar et al., 2016). In a separate validation cohort of 24 FASD and 24 control children (ages 3.5 to 18 years), 82 hypermethylated and 79 hypomethylated genes were detected, some the same as in the previous study (Lussier et al., 2018). The extent to which gene-specific methylation changes in buccal epithelial cells reflects upon global methylation in the nuclei of brain neurons is unknown.

In summary, we showed a variety of global epigenetic changes in brain cell nuclei of human fetuses and infants with a history of PNAE. These partially align with experimental PNAE studies in rodents. However, rapid developmental changes in the expression of specific DNA cytosine modifications and histone PTMs across ages, as well as environmental influences, make it difficult to translate observations in rodents to findings in humans. In general, our exploratory findings support the broad hypothesis that DNA and histone epigenetic changes occur in PNAE. These changes might contribute to the abnormalities in brain development that are associated with FASD. Future work will include detailed cell type analysis (e.g., with double-label immunofluorescence) to confirm specific cell populations affected by PNAE, in particular the heterogenous progenitor cells in the SVZ and the multiple cell types in the cerebral cortex. Eventually, we hope to correlate these global changes with gene-specific modifications in brain and perhaps in accessible nonneural tissues.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

RESEARCH INVOLVING HUMAN PARTICIPANTS AND/OR ANIMALS

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. For the human study, ethics approval was obtained from the Research Ethics Board at the University of Manitoba (#HS1311 – H2011:213). The Macaque Project was performed in the Infant Primate Research Laboratory (jointly operated by the University of Washington Regional Primate Research Center and the Child Development and Mental Retardation Center of the University of Washington Center on Human Development & Disability) in compliance with University of Washington Administrative Policy for the humane treatment of animals used in research.

INFORMED CONSENT

The tissues analyzed were selected retrospectively; the Research Ethics Board agreed that the potential for emotional harm to parents contacted about deceased children exceeded the risks of discovery about important unknown pathology.

AUTHORS' CONTRIBUTIONS

JSJ conducted almost all the research, put almost all results together, and wrote the manuscript. HS performed some of the Macaque immunostaining and imaging. DB analyzed oxidative changes in brain tissue and reprocessed the monkey brain tissue. SJA and SKC provided the Macaque brain samples and contributed to the discussion and final review of the manuscript. JRD provided guidance over the selection of markers and contributed to the discussion and final review of the manuscript discussion. MRD planned the project, provided financial support, effectuated the statistical analysis, and finalized the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Published epigenetic studies of brain tissue following ethanol exposure.

Table S1-1. Changes in DNA cytosine modifications and related enzymes following experimental in utero (not postnatal) alcohol exposure in the brain specifically.

Table S1-2. Histone post-translational modifications (PTMs) and enzymes associated with experimental in utero (not postnatal) alcoholexposure in the brain specifically.

Appendix S2. Experimental details of macaque PNAE model.

Table S2-1. Alcohol-exposed and control macaque details [1–3].

Appendix S3. Rationale for the selection of epigenetic marks (DNA cytosine modifications, histone acetylation and histone methylation) being investigated in PNAE human and macaque monkey brain samples.

Appendix S4. Procedural details of immunohistochemical labeling.

Appendix S5. Immunohistochemical stains showing total histone H3 and H4 epigenetic modifications.

Figure S5-1. Representative immunohistochemical detection of epigenetic marks in human control temporal neocortex showing discrepancies between selective and total histone antibodies.

Figure S5-2. Representative immunohistochemical detection of epigenetic mark H3K36me3 in human control ventricular (VZ) and subventricular zones (SVZ).

Figure S5-3. Representative immunohistochemical detection of epigenetic marks in human control vascular endothelial cells, arterial smooth muscle cells lining blood vessels, and epithelial cells of the choroid plexus.

Appendix S6. Proportion rank values representing specific brain cell types among the temporal ependyma, dentate

gyrus, temporal cortex and white matter in human control fetal and infant cases for each of the epigenetic marks studied.

Appendix S7. Representative photomicrographs showing immunohistochemical detection of 5fC and H3K27me3 epigenetic marks in control and PNAE macaque temporal horn ependyma.

Appendix S8. Lack of immunohistochemical evidence for oxidative damage in human and monkey brains with prenatal alcohol exposure.

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Twin study confirms virtually identical prenatal alcohol exposures can lead to markedly different fetal alcohol spectrum disorder outcomes—fetal genetics influences fetal vulnerability.

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Abstract

Background: Risk of fetal alcohol spectrum disorder (FASD) is not based solely on the timing and level of prenatal alcohol exposure (PAE). The effects of teratogens can be modified by genetic differences in fetal susceptibility and resistance. This is best illustrated in twins.

Objective: To compare the prevalence and magnitude of pairwise discordance in FASD diagnoses across monozygotic twins, dizygotic twins, full-siblings, and half-siblings sharing a common birth mother.

Methods: Data from the Fetal Alcohol Syndrome Diagnostic & Prevention Network clinical database was used. Sibling pairs were matched on age and PAE, raised together, and diagnosed by the same University of Washington interdisciplinary team using the FASD 4-Digit Code. This design sought to assess and isolate the role of genetics on fetal vulnerability/resistance to the

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Author contribution
All authors are members of the interdisciplinary FASD diagnostic team and participated in the interpretation and reporting of the study's outcomes. SJAH conducted the statistical analyses.

Ethical approval
This study was approved by the University of Washington Human Subjects Division.

teratogenic effects of PAE by eliminating or minimizing pairwise discordance in PAE and other prenatal/postnatal risk factors.

Results: As genetic relatedness between siblings decreased from 100% to 50% to 50% to 25% across the four groups (9 monozygotic, 39 dizygotic, 27 full-sibling and 9 half-sibling pairs, respectively), the prevalence of pairwise discordance in FASD diagnoses increased from 0% to 44% to 59% to 78%. Despite virtually identical PAE, 4 pairs of dizygotic twins had FASD diagnoses at opposite ends of the fetal alcohol spectrum—Partial Fetal Alcohol Syndrome versus Neurobehavioral Disorder/Alcohol-Exposed.

Conclusion: Despite virtually identical PAE, fetuses can experience vastly different FASD outcomes. Thus, to protect all fetuses, especially the most genetically vulnerable, the only safe amount to drink is none at all.

Keywords

fetal alcohol spectrum disorder; twins; genetics; prenatal alcohol exposure

Introduction

The effects of teratogens can be modified by genetic differences in fetal susceptibility and resistance [1]. Fetal alcohol syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of the teratogen alcohol during pregnancy. FAS is characterized by growth deficiency, a unique cluster of minor facial anomalies and central nervous system (CNS) structural and/or functional abnormalities. Not all fetuses exposed to and damaged by prenatal alcohol exposure (PAE) have FAS. The physical, cognitive, and behavioral deficits observed among individuals with PAE are not dichotomous, that is either normal or clearly abnormal. Rather, the outcomes all range along separate continua from normal to clearly abnormal [2]. This full range of outcomes caused by PAE is called Fetal Alcohol Spectrum Disorders (FASD). Diagnoses like FAS, Partial FAS (PFAS), Static Encephalopathy/Alcohol Exposed (SE/AE) and Neurobehavioral Disorder/Alcohol Exposed (ND/AE) fall broadly under the umbrella of FASD [2,3].

Fetal risk of damage from PAE is not just dependent on the timing, frequency, and quantity of exposure. Fetal alcohol spectrum disorders (FASD) are caused by a complex interaction of genes and environment, and are regulated by both parental and fetal genes [4]. Fetal genetics influences a fetus' vulnerability to the teratogenic effects of PAE [5]. In a 1993 study of 16 monozygotic and dizygotic twin pairs, Streissguth and Dehaene [6] reported 100% pairwise concordance in FASD diagnoses among monozygotic twin pairs, while dizygotic twins were only 64% concordant. The outcomes of that study strongly suggested that genetic loci regulate susceptibility to, or resistance against FASD. This 1993 study was conducted prior to the creation of rigorous FASD diagnostic systems. Patients were diagnosed as FAS or Fetal Alcohol Effects. If two fetuses exposed to identical levels of alcohol can experience vastly different FASD outcomes, this would have important implications for public health messaging and the setting of exposure thresholds in FASD diagnostic guidelines.

The purpose of this study was to compare the prevalence and magnitude of pairwise discordance in FASD diagnoses across four groups of sibling pairs: monozygotic twins, dizygotic twins, full-siblings, and half-siblings sharing a common birth mother. All sibling pairs had virtually identical or reportedly similar levels of PAE, were raised together, were diagnosed by the same interdisciplinary team using the 4-Digit Diagnostic Code and were identical or similar in age at the time of diagnosis. This sibling-pair design sought to more fully assess and isolate the role of genetics on fetal vulnerability to the teratogenic effects of PAE by eliminating or minimizing pairwise discordance in age, PAE and other prenatal and postnatal risk factors.

Specific Aims:

1. To determine if the prevalence of FASD diagnostic discordance was higher among dizygotic twin pairs than among monozygotic twin pairs.
2. To determine if the prevalence of FASD diagnostic discordance increases as the proportion of genome shared between sibling-pairs decreases across the four study groups: monozygotic twins, dizygotic twins, full-siblings, and half-siblings sharing a common birth mother.
3. To document the greatest magnitude of FASD diagnostic discordance observed between twin pairs with virtually identical PAE. Can twins with virtually identical PAE present at opposite ends of the fetal alcohol spectrum?
4. To estimate the proportion of phenotypic variance in FASD diagnoses due to genetic factors (heritability).

Methods

A retrospective study was conducted using data collected from twin and sibling pairs that received a FASD diagnostic evaluation at the University of Washington Fetal Alcohol Syndrome Diagnostic & Prevention Network (FASDPN).

FASD Diagnostic Method:

FASD diagnoses were rendered using the FASD 4-Digit Diagnostic Code. It is described in full by Astley [2, 7, 8]. Briefly, the 4 digits of the FASD 4-Digit Code reflect the magnitude of expression of the 4 key diagnostic features of FASD, in the following order: 1) growth deficiency, 2) FAS facial phenotype, 3) CNS structural/functional abnormalities, and 4) PAE (Figure 1). The magnitude of expression of each feature is ranked independently on a 4-point Likert scale, with 1 reflecting complete absence of the FASD feature and 4 reflecting a strong “classic” presence of the FASD feature. Each Likert rank is specifically case defined. There are a total of 102 4-Digit Codes that fall broadly under the umbrella of FASD. These codes cluster under four clinically meaningful FASD diagnoses: fetal alcohol syndrome (FAS) (4-Digit Code Diagnostic Categories A, B): Partial FAS (PFAS) (Diagnostic Category C); Static Encephalopathy/Alcohol-Exposed (SE/AE) (Diagnostic Categories E, F); and Neurobehavioral Disorder/Alcohol-Exposed (ND/AE) (Diagnostic Categories G, H) (Figure 1). Individuals that did not meet criteria for one of these FASD diagnostic classifications were identified in this study as Not FASD/Alcohol-Exposed (Diagnostic Categories I, J).

Study Groups:

The sibling pairs were partitioned into four study groups: 1. monozygotic twins, 2. dizygotic twins, 3. full-siblings, and 4. half-siblings sharing a common birth mother. Monozygotic twin pairs share virtually 100% of their genome. Dizygotic and full-sibling pairs share, on average, 50% of their genome. Half-sibling pairs with a common birth mother share, on average, 25% of their genome [9].

Data from all twin and sibling pairs that met the following inclusion criteria were used in this study:

- Sibling pairs were monozygotic twins, dizygotic twins, full-siblings, or half-siblings sharing the same birth mother.
- Both siblings received an FASD diagnostic evaluation at an FASDPN clinic by the same interdisciplinary team using the 2004 FASD 4-Digit Diagnostic Code.
- Siblings did not present with another genetic syndrome.
- Age at diagnosis could range from newborn to adult. Effort was made to select pairs that both fit into one of three age ranges at the time of diagnosis (0–3 years, 4–8 years, 9 or more years). This minimized the chance that FASD diagnostic contrasts between pairs may be due to one sibling being too young to fully assess or comparably assess brain function.
- All siblings had confirmed PAE. Twin pairs, by definition, had virtually identical PAE. Full sibling pairs and half-sibling pairs had to have concordant Alcohol Ranks (e.g., both siblings had to have Rank 3 alcohol exposure or both had to have Rank 4 alcohol exposure).
- Effort was made to select siblings raised together who experienced identical or similar other prenatal and postnatal risk factors.
- Siblings could be of any gender or race.

Data Set:

All data collected during an FASD diagnostic evaluation at the FASDPN are entered into the FASDPN database with patient consent and University of Washington Human Subjects Division approval. Approximately 3,000 patients have been evaluated in the clinic to date. The data document patient demographics, PAE, all other reported prenatal and postnatal adverse exposures and events and measures of growth, facial features, and structural and/or functional brain abnormalities used to derive the FASD 4-Digit Code. These data are recorded on three standardized diagnostic forms: the New Patient Information Form, FASD Diagnostic Form, and FAS Facial Photographic Analysis Report posted on the FASDPN website www.FASDPN.org [2, 8].

Key data used in this study included the patient's FASD 4-Digit Code, FASD diagnostic category (FAS, PFAS, SE/AE, ND/AE and Not FASD/AE), and their Growth, Face, CNS and Alcohol Ranks (Figure 1). The CNS Rank in the 4-Digit Code serves two purposes: 1) Ranks 1 through 4 document the probability of underlying CNS structural abnormality

(Rank 1: unlikely; Rank 2: possible; Rank 3: probable; and Rank 4: definite). 2) Ranks 1 through 3 also document the magnitude of CNS dysfunction as measured using standardized neuropsychological tools (Rank 1: no dysfunction; Rank 2: moderate dysfunction; and Rank 3 severe dysfunction). The CNS functional Ranks 1–3 introduced by the 4-Digit Code were case-defined to predict increasing likelihood of structural CNS abnormality—a predictive correlation that was subsequently confirmed through magnetic resonance imaging [7]. To distinguish these two CNS measures in the current study, they are labeled CNS1–4 and CNS1–3. PAE is ranked by the 4-Digit Code on a 4-point Likert scale (Figure 1A). Only subjects with Rank 3 or Rank 4 PAE were enrolled in this study. An Alcohol Rank 4 is assigned when PAE is confirmed and reported to be high risk (generally high peak blood alcohol concentrations delivered at least weekly in early pregnancy). An Alcohol Rank 3 is assigned when PAE is confirmed, but the amount reported is low to moderate risk (designated as PAE Rank 3b in this study) or the details on the amount and timing are unknown (designated as PAE Rank 3a in this study). The information used to generate the Alcohol Rank is presented on page 8 of the 4-Digit Code FASD Diagnostic Form [2]. In preparation for a FASD diagnostic evaluation, efforts are made to document the quantity, frequency and timing of maternal alcohol use before and during the index pregnancy. Although 99.5% of patients evaluated at the FASDPN clinic have confirmed PAE, only 30 to 40% have quantity, frequency and/or timing of exposure detailed in their records [10]. Recall error and reporting bias likely impact the accuracy of this more detailed information, therefore the more global measure of PAE “Alcohol Rank” was used as the primary measure of PAE risk in this study. In addition to the risk posed by PAE, measures of other prenatal and postnatal risks were also used in this study. Other prenatal risk factors documented in the FASDPN clinical database include poor prenatal care, pregnancy complications, presence of other syndromes/genetic abnormalities, and prenatal exposure to other substances (e.g., medications, tobacco, illicit drugs, and/or other teratogens). The 4-Digit Code ranks the magnitude of these other prenatal risks in a single composite measure labeled “Other Prenatal Risks Rank”. Rank 1 equals no risk; Rank 2 equals unknown risk; Rank 3 equals some risk; and Rank 4 equals high risk. Rank 4 is assigned when there is exposure to another teratogen (e.g., Dilantin) or when another syndrome or genetic condition is present (e.g., down syndrome, Fragile X, etc.). Rank 3 is assigned to all other prenatal risks. Postnatal risk factors documented in the FASDPN database include perinatal complications, number of home placements, physical and/or sexual abuse, neglect, and trauma. The 4-Digit Code ranks the magnitude of these other postnatal risks in a single composite measure labeled “Other Postnatal Risks Rank”. Rank 1 equals no risk; Rank 2 equals unknown risk; Rank 3 equals some risk; and Rank 4 equals high risk. Rank 4 is used to note severe postnatal circumstances that have been shown to have a significant adverse effect on development in most instances. Examples include physical/sexual abuse, multiple home placements, trauma, and severe neglect) [2]. Rank 3 is used to note conditions akin to those in Rank 4, but the circumstances are less severe.

Statistical Analyses:

The primary focus of the study was to compare the prevalence of discordant FASD diagnoses between sibling pairs across the 4 study groups. Descriptive statistics (means, SD, and proportions expressed as valid percentages (e.g., subjects with missing data are not

included in the denominator)) were used to profile the demographic and clinical outcomes of the 4 study groups. The chi-square test with tests for linear trend was used to compare proportions between the study groups. One-way ANOVA was used to compare outcomes measured on a continuous scale between the study groups. Two-tailed p-values < 0.05 were interpreted as statistically significant.

Heritability is formally defined as the proportion of phenotypic variation that is caused by genotypic variation in a population. FASD is not a genetic disorder, but fetal genetics appears to modify the teratogenic effects of PAE [5, 6]. Heritability has historically been estimated from studies of twins. Monozygotic twin pairs share essentially 100% of their genome. Dizygotic twin pairs share, on average, 50% of their genome. If a trait appears to be more similar in monozygotic twins than in dizygotic twins (when the twin pairs were raised together in the same environment), genetic factors likely play an important role in determining (or modifying) that trait. By comparing a trait in monozygotic twins versus dizygotic twins, one can calculate an estimate of its heritability. Heritability estimates range from 0% to 100%. A heritability close to 0% indicates that almost all of the variability in a trait is due to environmental factors (e.g., PAE and other prenatal and postnatal risk factors), with very little influence from genetic differences. A heritability estimate close to 100% indicates that almost all of the variability in a trait comes from genetic differences, with very little contribution from variability in environmental factors. When a phenotype is determined by a combination of genetic and environmental factors, heritability will be somewhere between 0% and 100%. Comparing discordance for monozygotic versus dizygotic twins allows an indirect estimate of the importance of genetic factors in producing the phenotype. Heritability estimates based on twin discordance studies can be simplistically viewed as: percent heritability = ((dizygotic discordance minus monozygotic discordance)/dizygotic discordance)*100 [9, 11]. It is important to understand that heritability does not indicate what proportion of a trait is determined by genes and what proportion is determined by environment. A heritability of 80% does not mean that a trait is 80% caused by genetic factors; it means that 80% of the variability in the trait in a population is due to genetic differences. Heritability measures the fraction of variation between individuals in a population that is due to their genotypes.

Results

Demographic and Clinical Profiles of the Four Study Groups

The study selection criteria generated 84 sibling pairs broken into four study groups (monozygotic twins, dizygotic twins, full siblings and half sibling sharing the same birth mother) with key factors that defined and differentiated the groups (Table 1).

The demographic and FASD diagnostic profiles of the study sample (Table 2) were highly representative of the entire FASDPN clinic population (n = 3,000) from which it was selected [10]. The gender and age distributions were comparable between the 4 study groups. Race was 100% concordant across all 84 twin/sibling pairs. The number of full and half sibling pairs included in the study may appear smaller than one would expect from a patient population of 3,000. A number of factors inherent in the FASDPN clinical dataset limited the number of full and half sibling pairs available for inclusion in the study. In

general, 85% of the patients evaluated by the FASDPN are in foster/adoptive care—no longer living with their birth parents. Confirmation of full or half sibling status requires knowledge of both birth parents' names. This is typically available on only half of the FASDPN patient population. Of the 54% (n = 1,617) with birth parent names available, 8% (n = 129) were siblings (full or half). Seventy-two of the 129 full and half siblings met the inclusion criteria for the study. The primary reason siblings failed to meet the study's inclusion criteria were they were too different in age (e.g., infant vs adolescent) at the time of their FASD evaluation to draw valid conclusions regarding the concordance/discordance of their diagnoses.

The matching criteria used to select twin and sibling pairs effectively minimized pairwise discordance in PAE and other prenatal and postnatal risk factors (Table 3). By definition, PAE was 100% concordant (virtually identical) between the monozygotic and dizygotic twin pairs. The Other Prenatal Risk Rank was 100% concordant between the monozygotic, dizygotic and full-sibling pairs, and 87.5% concordant between the half-sibling pairs. The Postnatal Risk Rank was highly concordant across all 4 groups (monozygotic: 100%; dizygotic: 87.2%; full-sibling: 91.3% and half-sibling: 75.0%), but did decrease linearly as the proportion of genome shared between siblings decreased.

Specific Aims 1 and 2: Pairwise concordance/discordance of FASD diagnostic outcomes

FASD diagnoses (FAS, PFAS, SE/AE, ND/AE, Not FASD/AE) were 100% concordant between monozygotic twin pairs, but only 56.4% concordant among dizygotic twin pairs (Table 4). This closely mirrored the proportion of the genome shared between twin pairs (monozygotic 100%; dizygotic 56%).

The prevalence of pairwise concordance in FASD diagnoses decreased significantly and linearly as the proportion of genome shared between siblings decreased across the 4 study groups (100% among 9 monozygotic twin pairs sharing 100% of their genome; 56.4% among 39 dizygotic twin pairs sharing 50% of their genome; 41.7% among 27 pairs of full-siblings sharing 50% of their genome; and 22.2% among 9 pairs of half-siblings sharing 25% of their genome) (Chi^2 linear trend = 1.7, p = 0.001) (Table 4, Figure 2).

When looking at the sub components that define FASD (growth deficiency, FAS facial phenotype, and CNS structural and/or functional abnormalities), the prevalence of pairwise discordance in the 4-Digit Rank for each of these components increased across the 4 groups as the proportion of genome shared between siblings decreased (Table 4, Figure 2). It is interesting to note that the prevalence of pairwise discordance in the Face Rank was the only component that increased significantly and linearly as the proportion of genome shared between siblings across the four groups decreased. The Rank 4 FAS facial phenotype, as defined by the 4-Digit Code, is the only component of FASD that is confirmed to be specific to (caused only by) PAE [7]. Other prenatal and postnatal risks can impact growth and brain development, but only PAE can cause the FAS facial phenotype. Thus, even though the prevalence of pairwise discordance in the Postnatal Risk Rank increased significantly across the 4 groups (monozygotic: 0%, dizygotic: 12.8%, full-sibling: 16.7%, and half-sibling: 25.0%) (Table 3, Figure 2), discordance in postnatal risk factors cannot influence the pairwise discordance observed in Face Ranks. It is also interesting to note that the

proportion of twin and sibling pairs within each study group that have the same (concordant) Face Ranks closely matches the proportion of the genome shared between the twin and sibling pairs within each study group (Figure 2).

There was no evidence in this study population that gender influenced the severity or pairwise discordance of FASD diagnostic outcomes. The severity of the FASD diagnosis was comparable between males and females across the entire study sample (n = 168) (Chi^2 = 5.4, p = 0.14).

Among the 19 dizygotic twins with discordant genders:

- The female had a more severe FASD outcome than the male in 31.6% of the pairs (6/19)
- The male had a more severe FASD outcome than the female in 26.3% of the pairs (5/19)
- The male and female had the same FASD outcome in 42.1% of the pairs (8/19)

Specific Aim 3: Magnitude of FASD diagnostic discordance between twin pairs

FASD Diagnostic Discordance: Since there was 100% diagnostic concordance between monozygotic twin pairs, this analysis focused on the 39 dizygotic twin pairs. Despite virtually identical PAE, 4 of the 39 dizygotic twin pairs had FASD diagnostic contrasts as large as PFAS vs ND/AE (Table 4). The sibling in each sibling pair with PFAS experienced severe CNS functional and/or structural abnormalities (i.e., the 3rd digit in their 4-Digit Code was Rank 3 or 4) while their co-twin experienced low to moderate CNS dysfunction (i.e., the 3rd digit in their 4-Digit Code was Rank 2). Two of these large contrasts occurred among same-sex dizygotic twins, (4334 vs 4324, 1434 vs 1224) and two occurred among mixed-gender dizygotic twins (4344 vs 2324, 1343 vs 1123). The four twin pairs had virtually identical PAE, were raised together, and had reportedly comparable prenatal and postnatal experiences (e.g., prenatal tobacco exposure, prenatal exposure to illicit drugs, multiple home placements, neglect, and/or physical/sexual abuse). In other words, their contrasts in FASD outcomes would appear to better-explained by their discordant genetic vulnerability to PAE, than their discordant environmental influences.

Four full-sibling pairs and one half-sibling pair also experienced large contrasts in FASD diagnoses (FAS vs ND/AE: 4-Digit Codes: 3443 vs 1223 and 3343 vs 1123) and PFAS vs ND/AE: 4-Digit Codes: 2434 vs 2324; 1443 vs 1323 and 2324 vs 4344) (Table 4). And like the dizygotic twins described above, these five sibling pairs had the same Prenatal Alcohol Ranks, were raised together, and had reportedly comparable prenatal and postnatal experiences (e.g., prenatal tobacco exposure, prenatal exposure to illicit drugs, multiple home placements, neglect, and/or physical/sexual abuse). Once again, their contrasts in FASD outcomes would appear to better-explained by their discordant genetic vulnerability to PAE, than their discordant environmental influences.

FAS Facial Phenotype Discordance: The 4-Digit Code ranks the magnitude of expression of the FAS facial phenotype on a 4-point Likert scale (Rank 1: absent; Rank 2:

mild; Rank 3: moderate; Rank 4: severe) (Figure 1A). As the proportion of genome shared between siblings decreased from 100% to 50% to 50% to 25% across the four groups (9 monozygotic, 39 dizygotic, 27 full-sibling and 9 half-sibling pairs, respectively), the prevalence of pairwise discordance in the FAS Facial Rank increased from 0.0% to 25.6% to 29.6% to 55.6% (Table 4). The prevalence of concordance in Facial Rank across the four groups closely followed the proportion of genome shared between siblings across the four groups (Figure 2).

Since the Rank 4 FAS facial phenotype, as defined by the 4-Digit Code, is the only FASD physical feature confirmed to be highly specific to (caused only by) PAE [7] it is interesting to document the prevalence of pairwise discordance (if any) involving the Rank 4 FAS facial phenotype (Table 4).

Two of the nine monozygotic twin pairs presented with the Rank 4 FAS facial phenotype. Both twins in each pair presented with concordant Rank 4 faces. Three of the 39 dizygotic twin pairs presented with the Rank 4 FAS facial phenotype; two pairs presented with concordant Rank 4 facial phenotypes and one pair presented with discordant Face Ranks (Rank 4 vs Rank 2). One twin in the discordant dizygotic twin pair presented with PFAS and a Rank 4 FAS facial phenotype. All three facial features of FAS were present—short PFLs, smooth philtrum and thin upper lip (mean PFL z-score −3.5, philtrum smoothness Rank 5, upper lip thinness Rank 4). In contrast, the co-twin presented with ND/AE and a Rank 2 Facial Phenotype. Only one of the three FAS facial features was present—a thin upper lip (mean PFL z-score −1.8, philtrum smoothness Rank 3, upper lip thinness Rank 4).

The Rank 4 facial phenotype was also observed among full-siblings and half-siblings (Table 4). Three of the 27 full-sibling pairs presented with the Rank 4 facial phenotype—all three pairs were discordant (Face Ranks 2 vs 4 and Face Ranks 3 vs 4). The Rank 4 facial phenotype was also observed in two of the 9 half-sibling pairs—both pairs had discordant Face Ranks (Face Ranks 2 vs 4). Even though the Alcohol Ranks were concordant for each of these five full-sibling and half-sibling pairs, this does not ensure that the day-to-day level of PAE was identical between each sibling pair.

Specific Aim 4: Heritability

Comparing pairwise discordance in FASD outcomes for monozygotic versus dizygotic twins allows an indirect estimate of the importance of genetic factors in modifying the teratogenic effects of PAE in this study sample. Percent heritability (((dizygotic discordance minus monozygotic discordance)/dizygotic discordance)*100) for different FASD outcomes in the current study were as follows:

- **FASD diagnosis** (FAS, PFAS, SE/AE, ND/AE, Not FASD/AE)

  ((0.436 – 0.00) / 0.436)*100 = **100%**
- **FAS Facial Rank**:

  ((0.256 – 0.0) / 0.256)*100 = **100%**
- **Growth Rank**

((0.436 – 0.111)/0.436)*100 = **74.5%**

- **CNS 1–4 Rank**

  ((0.436 – 0.111)/0.436)*100 = **74.5%**

Monozygotic twin pairs in this study had virtually identical genomes and virtually identical PAE. Under those genetic-environmental conditions, their FASD diagnoses and FAS facial phenotype Ranks were identical (0% discordant). In contrast, the dizygotic twin pairs in this study had virtually identical PAE, but shared only 50% of their genomes. Under those genetic-environmental conditions, 43.6% of the twin pairs had discordant FASD diagnoses and 25.6% had discordant FAS Facial phenotype Ranks. Based on these discordance rates for the monozygotic and dizygotic twin pairs, heritability estimates for the FASD diagnosis and the FAS Facial Rank were both 100%. In other words, essentially all of the discordance observed between twin pairs for these two outcomes appears to be due to differences in their genotypes, not differences in their environmental risk factors.

Heritability estimates for the Growth Rank and the CNS 1–4 Rank were both 74.5%, signifying that the Growth and CNS Ranks were determined by a combination of genetic and environmental factors. Although the prenatal environmental factor PAE was virtually identical between the twin pairs, PAE was not the only environmental risk factor in this study that could adversely impact growth and CNS development. Other prenatal risk factors like prenatal exposure to tobacco and other illicit drugs can impact growth and CNS development, but they, like PAE were virtually identical between the twin pairs. Thus, it is unlikely that these other prenatal risk factors explain the discordance in growth and CNS development observed between the twin pairs. On the other hand, postnatal environmental risk factors like neglect, abuse, and multiple home placements can adversely impact a child's growth and CNS development and did vary slightly between the dizygotic twin pairs—5 of the 39 dizygotic pairs had discordant Postnatal Risk Ranks (Table 3). But a much higher number of dizygotic pairs had discordant Growth Ranks (n = 17) and discordant CNS 1–4 Ranks (N = 17) (Table 4). More specifically, not all 5 dizygotic pairs with discordant Postnatal Risk Ranks had discordant Growth or CNS 1–4 Ranks. Only 2 of the 5 pairs had discordant Growth Ranks and only 3 of the 5 pairs had discordant CNS 1–4 Ranks. Stated another way, only 2 (12%) of the 17 dizygotic pairs with discordant Growth Ranks had discordant Postnatal Ranks, and only 3 (18%) of the 17 dizygotic pairs with discordant CNS1–4 Ranks had discordant Postnatal Ranks. Thus, as the heritability estimates suggest, variations in the Growth and CNS 1–4 Ranks appeared to be influenced by both genetic and environmental factors. Overall, the heritability estimates generated for the growth (74.5%), FAS face (100%) and CNS (74.5%) components of FASD are reflective of the fact that growth and CNS development are susceptible to a multitude of prenatal and postnatal environmental risk factors, whereas the FAS facial phenotype is highly specific to early prenatal exposure to alcohol.

If fetal genotype is modifying the teratogenic impact of PAE, the prevalence of pairwise concordance across FASD outcomes would more closely reflect the percent of genome shared between sibling pairs than the pairwise concordance of PAE and other prenatal and postnatal risk factors. This is illustrated graphically In Figure 2 (and Table 4). Monozygotic

twins, dizygotic twins, full siblings and half siblings share on average 100%, 50%, 50% and 25% of their genome respectively as depicted by the first set of bars. The pattern of pairwise concordance reflected in the bars for each FASD outcome more closely resemble the pattern of bars for Genome Shared than the patterns of bars reflecting pairwise concordance in Alcohol Rank, other Prenatal Risks, or Postnatal Risks. Since the FAS facial phenotype, as defined by the 4-Digit Code, is so highly specific to (caused only by) PAE, the most compelling evidence supporting the role genetics plays in modifying the teratogenic impact of PAE is illustrated in how highly correlated the bar patterns are between Genome Shared and Face Rank-and how poorly correlated the bar patterns are between Face Rank and Alcohol Rank (especially between monozygotic and dizygotic twin pairs with virtually identical PAE).

Discussion

Fetal genotype modifies the teratogenic effects of PAE:

The outcomes of this study provide conclusive evidence that fetal genotype can modify the teratogenic effects of PAE. When twin pairs with virtually identical PAE were genetically identical, their FASD diagnoses were identical. When twin pairs with virtually identical PAE were genetically different, their FASD diagnoses were often different (44% presented with discordant FASD diagnoses). And when their diagnoses were discordant, the magnitude of discordance was extreme 10% of the time. For example, four of the 39 pairs of dizygotic twins were born at opposite ends of the fetal alcohol spectrum (PFAS and ND/AE), despite virtually identical PAE. Finally, as the proportion of genome shared between siblings decreased from 100% to 50% to 50% to 25% across the four study groups (monozygotic, dizygotic, full-sibling and half-sibling pairs respectively), the prevalence of pairwise discordance in FASD diagnoses increased linearly from 0% to 44% to 59% to 78%.

The prevalence of pairwise concordance in FASD diagnoses observed in our 48 twin pairs (monozygotic 100%, dizygotic 56%) was comparable to the prevalence of concordance observed in 16 twin pairs (monozygotic 100%, dizygotic 64%) reported by Streissguth and DeHaene [6] back in 1993—the only other FASD twin group study published to date. The 16 twin pairs (5 monozygotic and 11 dizygotic) were born to alcohol-abusing mothers from two countries (the United States and France). The study population included 11 Caucasian and 5 Native American twin pairs ranging in age from 1.5 to 30 years. The study was conducted prior to the creation of rigorous, case-defined FASD diagnostic systems. Patients were diagnosed as FAS or Fetal Alcohol Effects (FAE) in accordance with gestalt approach to diagnosis published by Clarren and Smith in 1978 [12]. Thirty-nine percent had FAS, 19% had FAE and 42% were alcohol exposed but unaffected. The higher concordance observed in their dizygotic twin pairs will be due in part to the fact that concordance in a study using only two FASD diagnoses (FAS and FAE) will always be higher than concordance in a study using 4 FASD diagnoses (FAS, PFAS, SE/AE, and ND/AE). Over the years, the outcomes of ten additional twin pairs with PAE have been published as single-case studies [13–20]. Formal FASD diagnostic evaluations were rarely conducted, but the clinical descriptions of the twin pairs were consistent with monozygotic twin pairs having more concordant outcomes than dizygotic twin pairs.

Similar to humans, evidence of genetic modification of FASD outcomes also come from animal studies. For example, a study by Debelak and Smith [21] examined 11 genetic strains of chick embryos following ethanol exposure during early neurulation and found that the strains could be classified into very sensitive, moderately sensitive, or insensitive to ethanol-induced apoptosis of cranial neural crest cells, which give rise to facial structures. Comprehensive reviews on the genetics of FASD are presented by Mead and Sarkar [4] and Eberhart and Parnell [5].

Discordance in the FAS facial phenotype:

It is interesting to note the rather high prevalence of pairwise discordance (43.6%) in FASD diagnoses among dizygotic twins in this study, despite virtually identical PAE. It is clear that discordance in PAE does not explain their discordant FASD diagnoses, but are there factors other than PAE that may explain the discordance? FASD is characterized by growth deficiency, a specific cluster of minor facial anomalies, and abnormal CNS structure and/or function. Only the Rank 4 FAS facial phenotype, as defined by the 4-Digit Code, is confirmed to be specific to (caused only by) PAE [7]. The FAS facial phenotype is not caused by other prenatal and postnatal risk factors. In contrast, growth deficiency and CNS structural/functional abnormalities can be caused by a multitude of other prenatal and postnatal risk factors. Despite efforts to minimize postnatal contrasts between the twin pairs in this study (Table 3, Figure 1), some of the pairwise discordance in growth and CNS outcomes used to generate the FASD diagnoses is likely explained, in part, by discordant postnatal risk factors.

Documenting the prevalence of discordance (if any) for the Rank 4 FAS facial phenotype is of particular interest because the Rank 4 FAS facial phenotype is so highly specific to PAE [7]. If identical PAE can result in discordant Rank 4 facial phenotypes between twin pairs, this would further strengthen the evidence that genes are modifying the teratogenic impact of PAE. Since the FAS facial phenotype requires PAE in a very narrow window of time (during the gastrulation period of fetal development) [22, 23], the only pairwise discordance in Rank 4 facial phenotypes that would be meaningful (that could be validly interpreted) would be among monozygotic and dizygotic twin pairs—the only two groups where the timing of PAE can be confirmed to be virtually identical on a day-to-day basis between twin pairs.

Two of the nine monozygotic twin pairs presented with Rank 4 FAS facial phenotypes. Both twins in each pair presented with concordant Rank 4 faces. Three of the 39 dizygotic twin pairs presented with Rank 4 FAS facial phenotypes; two pairs presented with concordant Rank 4 faces and one pair presented with discordant Face Ranks (Rank 4 vs Rank 2). The twin pair with discordant Face Ranks presented as follows: Twin 1: PFAS, Face Rank 4, all three of the FAS facial features (mean PFL z-score −3.5, philtrum smoothness Rank 5, upper lip thinness Rank 4). Twin 2: ND/AE, Face Rank 2, only 1 of the 3 FAS facial features—a thin upper lip (mean PFL z-score −1.8, philtrum smoothness Rank 3, upper lip thinness Rank 4). The work by Das et al., [24], presented below, provides a compelling genetic explanation for why Face Ranks were always concordant among monozygotic twins, but occasionally discordant among dizygotic twins.

Das et al., [24] reported a significant gene-environment interaction explaining variation in facial morphology associated with ethanol use in pregnancy. Genetic diversity in ethanol metabolizing enzymes occurs in the general population. Ethanol is metabolized to acetaldehyde by two enzyme systems: the microsomal ethanol oxidizing system and alcohol dehydrogenase (ADH) [25, 26]. The presence of the ADH1B*3 allele has been found to be protective for offspring neurodevelopmental and growth outcome after maternal ethanol consumption in pregnancy [27]. In 2004, Das et al [24] demonstrated that among African American women and their offspring, the presence of an ADH1B*3 allele was protective for the effects of maternal ethanol ingestion during pregnancy on infant facial formation. The protective effect demonstrated was present with the allele present in only the mother, only the infant, or both the mother and the infant. Exposure to ethanol and absence of the ADH1B*3 allele in both the mother and infant resulted in significant reductions in three facial measurements obtained from infant facial photographs-palpebral fissure length, inner canthal distance and the distance from the bridge of the nose to the bottom of the upper lip. Based on the findings of Das et al., [24] one could speculate that discordant FAS Face Ranks could occur in dizygotic twins (as observed in our study) if the ADH1B*3 allele was absent in the mother and one twin, but present in the other twin. Based on the same line of reasoning, one would expect monozygotic twins to always present with concordant Face Ranks (as was observed in our study). Replication of the Das et al., study using a study population of monozygotic and dizygotic twins with PAE would greatly advance our understanding how the ADH1B*3 allele modifies the teratogenic impact of PAE.

Implications for public health messaging and setting FASD diagnostic exposure thresholds:

Despite virtually identical PAE, 4/39 (10%) dizygotic twin pairs had FASD diagnostic contrasts as large as PFAS vs ND/AE. The four twin pairs had virtually identical PAE, were raised together, and had reportedly identical prenatal and postnatal experiences (e.g., prenatal tobacco, illicit drug exposure, home placements, physical/sexual abuse). In other words, their contrasts in FASD outcomes would appear to better-explained by their discordant genetic vulnerability to PAE, than their discordant environmental influences. These 4 twin pairs provide powerful evidence that what may be construed in public health messaging (and some FASD diagnostic guidelines [28–30] as a safe level of exposure for one fetus, may very well place another fetus at significant risk. Not only can the same level of PAE cause strikingly different outcomes in two fetuses, but PAE reportedly below the threshold of exposure required by some FASD diagnostic guidelines can result in full FAS (See Figure 9 in Astley, et al., [31]). Thus, as stated by the U.S. Centers for Disease Control and Prevention [32] “*There is no guaranteed safe level of alcohol use at any time during pregnancy. Fetal alcohol spectrum disorders are completely preventable if a woman does not drink during pregnancy.”*

Potential Limitations

Zygosity Classification:

Twins were classified as monozygotic or dizygotic for this study based on clinical and social service records shared with the FASDPN clinic at the time of their FASD evaluation. It is

unknown how many twin pairs had zygosity confirmed through DNA genotyping. While there remains a small chance that one or more twin pairs in this study have their zygosity misclassified, a study of 578 twin pairs conducted by the National Academy of Sciences found parent report of zygosity was confirmed accurate by DNA genotyping over 95% of the time [33]. When misclassification occurred, it was most likely to occur among monozygotic twins who were not strikingly similar in appearance and thus incorrectly classified as dizygotic. This direction of error would lead to more conservative estimates of heritability. In the current study, all monozygotic twins looked identical and all dizygotic twins were easily distinguished from one another.

Do twins share identical prenatal environments?

Not necessarily. It is for that reason the prenatal environments and PAE shared between our 48 twin pairs is described throughout this study as virtually identical. How twins experience the prenatal environment depends, in part, on chorionicity, i.e., whether twins share a single chorion (monochorionic) or have separate chorions (dichorionic). Monozygotic twins can be mono- or dichorionic, whereas dizygotic twins are dichorionic [34]. The chorionicity of the 9 monozygotic twin pairs in the current study was unknown. The chorion is the outer-most fetal membrane that contains the amnion/amniotic sac. The amnion is the thin inner-most fetal membrane that protects the embryo/fetus and contains amniotic fluid. The chorion connects the amnion, amniotic sac, and the fetus to the placenta and contributes to placental development. Thus, if twins share a chorion (e.g., are monochorionic) they will share a single placenta, whereas twins with separate chorions (e.g., dichorionic) develop individual placentas. Dizygotic twins are dichorionic, since they form from two separately fertilized eggs. Among Caucasian populations, total twinning rates were estimated at 15–16 per 1,000 in 2003 [35]. In Caucasian populations, monozygotic twins comprise ~26% of all twins. For Caucasian populations about 17% of all twin pairs are monozygotic-monochorionic, ~9% are monozygotic-dichorionic and ~74% are dizygotic-dichorionic. All twins can be expected to have many kinds of in-utero differences, such as placental flow in monozygotic twins and the amount of microchimerism in dizygotic twins [36]. The greatest risk associated with monochorionic placentation is related to the structure of blood vessels. One twin typically has better placement and therefore receives more of the nutrients [34]. The placenta also functions as a barrier, allowing small molecules (e.g., gases, nutrients, waste material, antibodies) to pass between mother and child through passive transport [37, 38]. Other small molecules that can impact fetal development (e.g., some maternal hormones like cortisol; bacteria; teratogens such as alcohol) can also be diffused through the placenta [37, 39]. Unequal placental sharing is a major cause of fetal growth discordance in monozygotic twins [40]. It is interesting to note that one of the few occurrences of discordant outcomes between monozygotic twins in the current study was discordant growth in one twin pair (Growth Rank 3 versus Growth Rank 1). Both twins had concordant weight percentiles (ranging from the 20th to 40th percentiles) at birth and 2 years of age. Height percentiles, however, were significantly discordant. One twin was significantly shorter (1st and 10th percentiles at birth and 2 years of age) than the other (20th and 60th percentiles at birth and 2 years of age). All in all, while prenatal environments, including level of PAE, are not necessarily 100% identical between twin pairs, the near perfect match between percent of genome shared and FASD diagnostic concordance (monozygotic twins: 100% genome

shared and 100% FASD concordance; dizygotic twins: 50% genome shared, 56% FASD concordance) suggests the prenatal -environments and PAE levels in our 48 twin pairs were virtually identical.

Conclusions

Not all fetuses are equally vulnerable to the adverse effects of prenatal alcohol exposure. Risk is not just dependent on timing and level of exposure. Fetal genetics plays an important role. As demonstrated in this study, despite virtually identical prenatal alcohol exposures, two fetuses can experience vastly different FASD outcomes. So which fetus is genetically vulnerable? We currently have no way of knowing. Thus, to protect all fetuses, especially the most genetically vulnerable, the only safe amount to drink is none at all.

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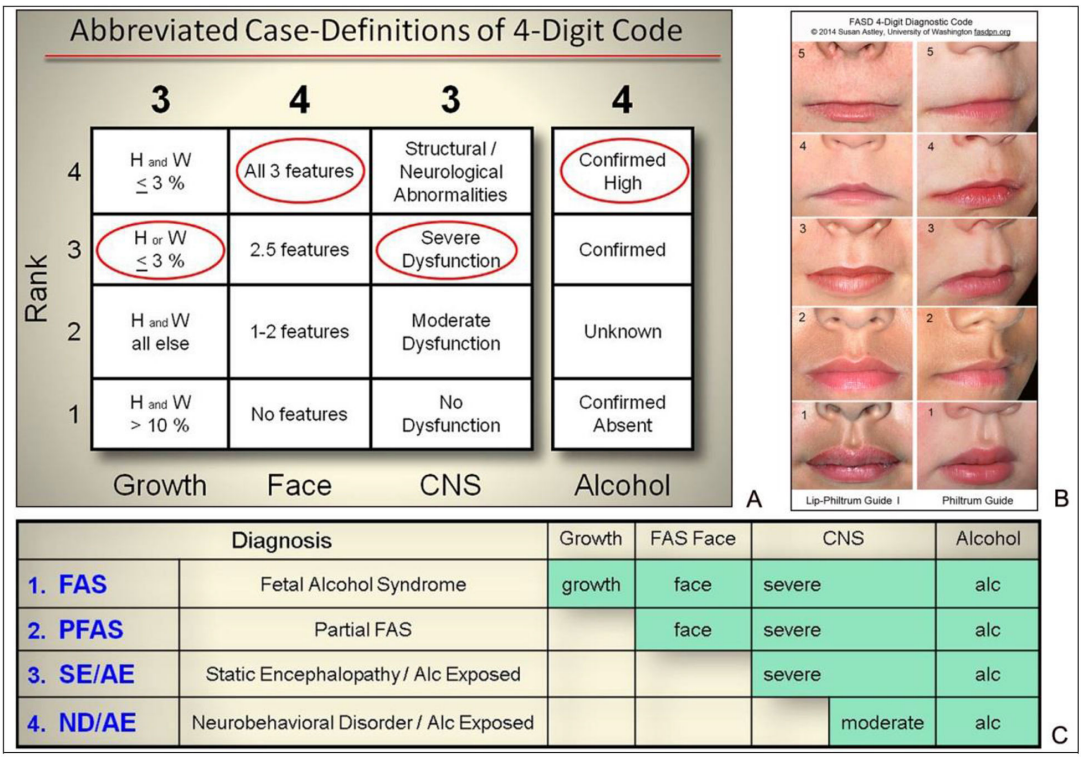

Diagnosis		Growth	FAS Face	CNS		Alcohol
1. FAS	Fetal Alcohol Syndrome	growth	face	severe		alc
2. PFAS	Partial FAS		face	severe		alc
3. SE/AE	Static Encephalopathy / Alc Exposed			severe		alc
4. ND/AE	Neurobehavioral Disorder / Alc Exposed				moderate	alc

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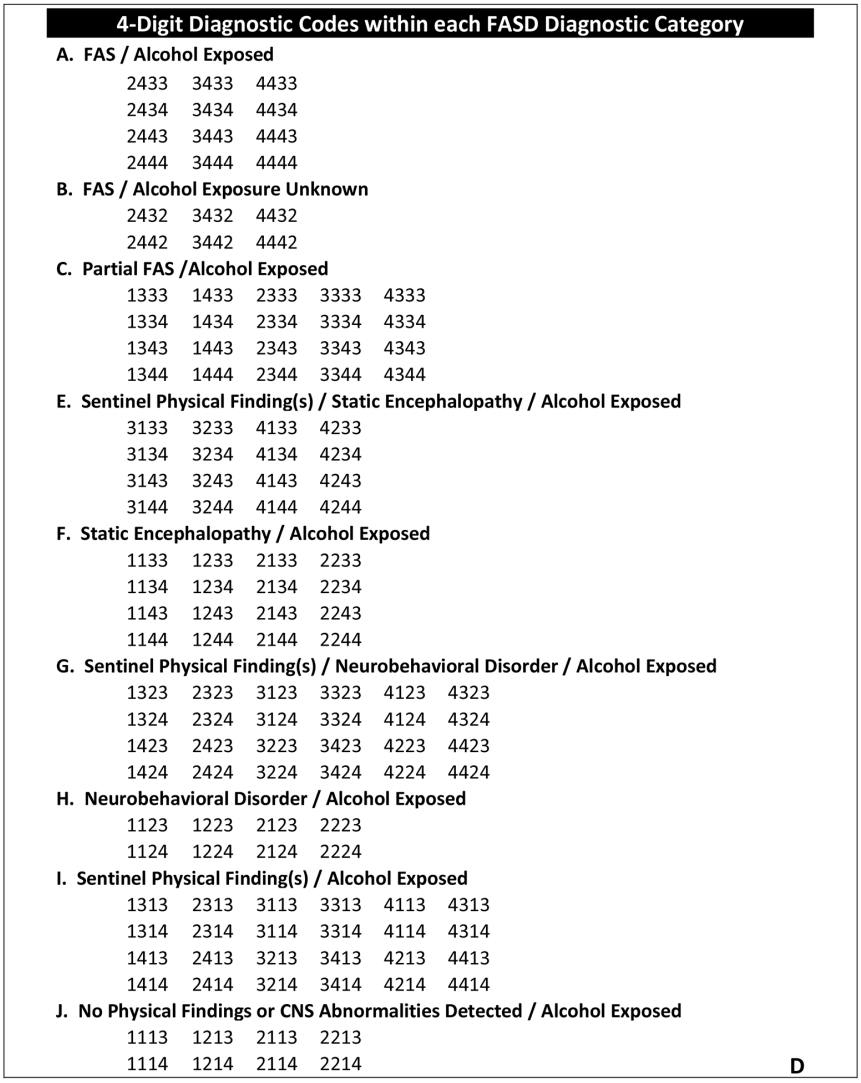

Figure 1. FASD 4-Digit Diagnostic Code.

A) Abbreviated case-definitions for the fetal alcohol spectrum disorder (FASD) 4-Digit Code [2]. The 4-Digit Code 3434 is one of 12 4-Digit Codes that fall under the diagnostic category FAS. **B)** The Rank 4 FAS facial phenotype requires 3 features: 1) palpebral fissure lengths 2 or more standard deviations below the mean; 2) a smooth philtrum (Rank 4 or 5 on the University of Washington Lip-Philtrum Guide); and 3) a thin upper lip (Rank 4 or 5 on the University of Washington Lip-Philtrum Guide). **C and D)** The 4-Digit Code produces four diagnostic subgroups under the umbrella of FASD: FAS (Diagnostic Categories A, B), PFAS (Diagnostic Category C), SE/AE (Diagnostic Categories E, F), and ND/AE (Diagnostic Categories G, H). Abbreviations: CNS: central nervous system; H: height percentile; W: weight percentile.

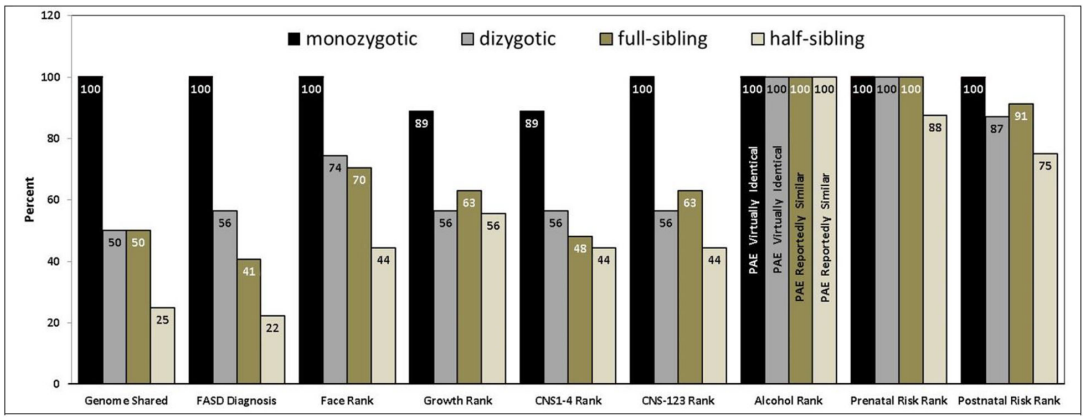

Figure 2. Twin/Sibling Pairwise Concordance in FASD outcomes and prenatal/postnatal risks.

Monozygotic twins, dizygotic twins, full siblings and half siblings share 100%, 50%, 50% and 25% of their genome respectively as depicted by the first set of bars. If fetal genetics is modifying the teratogenic impact of PAE, the pattern of pairwise concordance reflected in the bars for each FASD outcome will more closely resemble the pattern of bars for Genome Shared than the patterns of bars reflecting pairwise concordance in Alcohol Rank, other Prenatal Risks or Postnatal Risks. The bar patterns across all FASD outcomes are far more reflective of the pattern of bars for Genome Shared than the pattern of bars for Alcohol Rank, Prenatal Risk Rank or Postnatal Risk Rank. Although the bar pattern for Postnatal Risk Rank resembles the bar pattern for Face Rank, discordance in postnatal risk factors cannot be contributing to discordance in Face Rank because only prenatal factors can impact facial morphology. Since the FAS facial phenotype, as defined by the 4-Digit Code, is so specific to (caused only by) PAE, the most compelling evidence supporting the role genetics plays in modifying the teratogenic impact of PAE is illustrated in how highly correlated the bar patterns are between Genome Shared and Face Rank and how poorly correlated the bar patterns are between Face Rank and Alcohol Rank (especially between monozygotic and dizygotic twins with virtually identical PAE).

Table 1.

Key factors that defined and differentiated the 4 study groups.

Features shared between sibling pairs	Study Groups			
	1. Monozygotic twins	2. Dizygotic twins	3. Full-siblings	4. Half-siblings with the same birth mother
	9 pairs	39 pairs	27 pairs	9 pairs
Birth mother	identical	identical	identical	identical
Birth father	identical	identical	identical	different
Genome shared	~100%	~50%	~50%	~25%
Prenatal alcohol exposure	virtually identical	virtually identical	100% same Rank	100% same Rank
Other prenatal risks	virtually identical	virtually identical	100% same Rank	88% same Rank
Siblings raised together	100%	100%	96%	100%
Other postnatal risks	100% same Rank	87% same Rank	83% same Rank	75% same Rank
Matched in age within one of 3 age-ranges (0–3; 4–8, 9+ years)	100%	100%	*93%	*89%

* 2 pairs of full-siblings and 1 pair of half-siblings had one sibling that was in a younger age category. In each of these 3 pairs, the younger sibling had the more severe FASD diagnostic outcome.

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Table 2.

Comparison of demographic and FASD clinical profiles between the four study groups

Demographic and Clinical Characteristics	Monozygotic		Dizygotic		Full-siblings		Half-siblings		Total	
	N = 18 (9 pairs)		N = 78 (39 pairs)		N = 54 (27 pairs)		N = 18 (9 pairs)		N = 168 (84 pairs)	
Gender (N pairs; valid %)										
female-female	4	44.4	10	25.6	7	25.9	2	22.2	23	27.4
male-male	5	55.6	10	25.6	11	40.7	4	44.4	30	35.7
Mixed gender	0	0.0	19	48.7	9	33.3	3	33.3	31	36.9
Overall proportion of female subjects	8/18	44.4	37/78	47.4	23/54	42.6	7/18	38.9	75/168	44.6
Race (N; valid %)										
Caucasian	4	22.2	32	41.0	32	59.3	14	77.8	82	48.8
African American	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Native American	0	0.0	8	10.3	2	3.7	1	5.6	11	6.5
Hispanic	0	0.0	4	5.1	6	11.1	0	0.0	10	6.0
Mixed race: combinations of above races	14	77.8	34	43.6	14	25.9	3	16.7	65	38.7
Age at Diagnosis (years) (N, valid %)										
0–3.9	4	22.2	30	38.5	17	31.5	2	11.1	53	31.5
4–8.9	12	66.7	28	35.9	22	40.7	9	50.0	71	42.3
9–19.7	2	11.1	20	25.6	15	27.8	7	38.9	44	26.2
Sibling pairs raised together (N pairs; valid %)										
yes	9	100.0	39	100.0	26	96.3	9	100.0	83	98.8
Prenatal Alcohol Exposure: 4-Digit Alcohol Rank (N, valid %)										
Rank 3a: Exposure confirmed, amount unknown.	8	44.5	30	38.5	26	48.1	6	33.3	70	41.7
Rank 3b: Exposure confirmed, amount low to mod.	4	22.2	0	0.0	4	7.3	0	0.0	8	4.8
Rank 4: Confirmed and level high	6	33.3	48	61.5	24	44.4	12	66.7	90	53.5
Other Prenatal Risks: 4-Digit Rank (N, valid %)										
Rank 1: no risk	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Rank 2: unknown risk	2	11.1	8	10.3	0	0.0	2	11.1	12	7.1
Rank 3: moderate risk	16	88.9	70	89.7	54	100.0	15	83.3	155	92.3

Demographic and Clinical Characteristics	Monozygotic		Dizygotic		Full-siblings		Half-siblings		Total	
	N = 18 (9 pairs)		N = 78 (39 pairs)		N = 54 (27 pairs)		N = 18 (9 pairs)		N = 168 (84 pairs)	
Rank 4: high risk	0	0.0	0	0.0	0	0.0	1	5.6	1	0.6
Postnatal Risks: 4-Digit Rank (N, valid %)										
Rank 1: no risk	0	0.0	2	2.6	1	1.9	0	0.0	3	1.8
Rank 2: unknown risk	2	11.1	0	0.0	5	9.3	1	5.6	8	4.8
Rank 3: moderate risk	6	33.3	37	47.4	31	57.4	4	22.2	78	46.4
Rank 4: high risk	10	55.6	39	50.0	17	31.5	13	72.2	79	47.0
FASD Diagnoses (N, valid %)										
FAS	4	22.2	1	1.3	2	3.7	1	5.6	8	4.8
PFAS	0	0.0	5	6.4	3	5.6	2	11.1	10	6.0
SE/AE	8	44.5	15	19.2	12	22.2	5	27.8	41	24.4
ND/AE	4	22.2	48	61.5	23	42.6	9	50.0	84	50.0
Sentinel Physical Findings/AE	0	0.0	0	0.0	4	7.4	1	5.6	4	2.4
Not FASD/AE	2	11.1	9	11.5	10	18.5	0	0.0	21	12.5

Table 3.

Matching criteria effectively minimized pairwise discordance in PAE and other prenatal and postnatal risk factors.

Prenatal and Postnatal Risks	Monozygotic		Dizygotic		Full-siblings		Half-siblings	
	N = 18 (9 pairs)		N = 78 (39 pairs)		N = 54 (27 pairs)		N = 18 (9 pairs)	
	N Pairs	valid%	N Pairs	valid%	N Pairs	valid%	N Pairs	valid%
Prenatal Alcohol Exposure (PAE): 4-Digit Code Rank								
Concordant Ranks between sibling pairs								
Overall	9	100.0	39	100.0	27	100.0	9	100.0
Rank 1: Confirmed absence of PAE	0	0.0	0	0.0	0	0.0	0	0.0
Rank 2: PAE unknown	0	0.0	0	0.0	0	0.0	0	0.0
Rank 3a: PAE confirmed, amount unknown	4	44.5	15	38.5	13	48.1	3	33.3
Rank 3b: PAE confirmed, amount low to moderate	2	22.2	0	0.0	2	7.3	0	0.0
Rank 4: PAE confirmed, amount high	3	33.3	24	61.5	12	48.6	6	66.7
Discordant Ranks between sibling pairs								
Overall	0	0.0	0	0.0	0	0.0	0	0.0
Other Prenatal Risks: 4-Digit Code Rank								
Concordant Ranks between sibling pairs								
Overall	9/9	100.0	39/39	100.0	27/27	100.0	8/9	88.9
Valid Overall (excluding pairs with unknown risk)	8/8	100.0	35/35	100.0	27/27	100.0	7/8	87.5
Rank 1: no risk	0	0.0	0	0.0	0	0.0	0	0.0
Rank 2: unknown risk	1	11.1	4	10.3	0	0.0	1	11.1
Rank 3: some risk	8	88.9	35	89.7	27	100.0	7	77.8
Rank 4: high risk	0	0.0	0	0.0	0	0.0	0	0.0
Discordant Ranks between sibling pairs								
Overall	0/9	0.0	0/39	0.0	0/27	0.0	1/9	11.1
Valid Overall (excluding pairs with unknown risk)	0/9	0.0	0/39	0.0	0/27	0.0	1/8	12.5
Rank 4: high risk – Rank 3: some risk	0	0.0	0	0.0	0	0.0	1	11.1
Postnatal Risks: 4-Digit Code Rank								
Concordant Ranks between sibling pairs								
Overall	9/9	100.0	34/39	87.2	21/27	77.8	6/9	66.7

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Prenatal and Postnatal Risks	Monozygotic		Dizygotic		Full-siblings		Half-siblings	
	N = 18 (9 pairs)		N = 78 (39 pairs)		N = 54 (27 pairs)		N = 18 (9 pairs)	
	N Pairs	valid%	N Pairs	valid%	N Pairs	valid%	N Pairs	valid%
Valid Overall (excluding pairs with unknown risk)	8/8	100.0	34/39	87.2	20/23	91.3	6/8	75.0
Rank 1: no risk	0	0.0	1	2.6	0	0.0	0	0.0
Rank 2: unknown risk	1	11.1	0	0.0	1	3.7	0	0.0
Rank 3: some risk	3	33.3	16	41.0	13	48.1	0	0.0
Rank 4: high risk	5	55.6	17	43.6	7	26.0	6	66.7
Discordant Ranks between sibling pairs								
Overall	0/9	0.0	5/39	12.8	6/27	22.2	3/9	33.3
Valid Overall (excluding pairs with unknown risk)	0/8	0.0	5/39	12.8	3/23	13.0	3/8	25.0
Rank 3: some risk – Rank 2: unknown risk	0	0.0	0	0.0	2	7.4	1	11.1
Rank 3: some risk – Rank 1: no risk	0	0.0	0	0.0	1	3.7	0	0.0
Rank 3: some risk – Rank 4: high risk	0	0.0	5	12.8	2	7.4	2	22.2
Rank 4: high risk – Rank 2: unknown risk	0	0.0	0	0.0	1	3.7	0	0.0

Abbreviations: PAE: prenatal alcohol exposure

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Table 4.

Prevalence of FASD diagnostic concordance and discordance between twin and sibling pairs.

Concordance and Discordance in FASD Outcomes between Twin and Sibling Pairs	1. Monozygotic N = 18 (9 pairs)		2. Dizygotic N = 78 (39 pairs)		3. Full-siblings N = 54 (27 pairs)		4. Half-siblings (maternal) N = 18 (9 pairs)	
	N pairs	Valid %	N pairs	Valid %	N pairs	Valid %	N pairs	Valid %
Pairwise FASD Diagnoses (FAS, PFAS, SE/AE, ND/AE, Not FASD/AE)								
Concordant outcomes between sibling pairs								
Total concordant pairs	9	100.0	22	56.4	11	40.7	2	22.2
FAS-FAS	2	22.2	0	0.0	0	40.7	0	0.0
PFAS-PFAS	0	0.0	0	0.0	0	0.0	0	0.0
SE/AE-SE/AE	4	44.4	4	10.3	2	7.4	0	0..0
ND/AE-ND/AE	2	22.2	16	41.0	6	22.2	2	22.2
Not FASD/AE-Not FASD/AE	1	11.2	2	5.1	3	11.1	0	0.0
Discordant outcomes between sibling pairs								
*Total discordant pairs	0	0.0	17	43.6	16	59.3	7	77.8
FAS-PFAS	0	0.0	1	2.6	0	0.0.	0	0.0
FAS-SE/AE	0	0.0	0	0.0	0	0.0	1	11.1
#FAS-ND/AE	0	0.0	0	0.0	2	7.4	0	0.0
PFAS-SE/AE	0	0.0	0	0.0	1	3.7	1	11.1
#PFAS-ND/AE	0	0.0	4	10.3	2	7.4	1	11.1
SE/AE-ND/AE	0	0.0	7	17.5	5	18.5	4	44.4
SE/AE-Not FASD/AE	0	0.0	0	0.0	2	7.4	0	0.0
ND/AE-Not FASD/AE	0	0.0	5	12.8	2	7.4	0	0.0
Not FASD/AE-Not FASD/AE	0	0.0	0	0.0	2	7.4	0	0.0
Pairwise FASD Diagnostic Features								
Discordant outcomes between sibling pairs								
Growth Ranks 1–4	***1	11.1	17	43.6	10	37.0	4	44.4
**Face Ranks 1–4: Total discordant pairs	0	0.0	10	25.6	8	29.6	5	55.6
Face Rank 1 vs 4	0	0.0	0	0.0	0	0.0	0	0.0

Concordance and Discordance in FASD Outcomes between Twin and Sibling Pairs	1. Monozygotic		2. Dizygotic		3. Full-siblings		4. Half-siblings (maternal)	
	N = 18 (9 pairs)		N = 78 (39 pairs)		N = 54 (27 pairs)		N = 18 (9 pairs)	
	N pairs	Valid %	N pairs	Valid %	N pairs	Valid %	N pairs	Valid %
Face Rank 2 vs 4	0	0.0	1	2.6	1	3.7	2	22.2
Face Rank 3 vs 4	0	0.0	0	0.0	2	7.4	0	0.0
CNS Ranks 1–4: probability of structural abnormality (none, possible, probable, definite)	***1	11.1	17	43.6	14	51.9	5	55.6
Alcohol Ranks 3–4	0	0.0	0	0.0	0	0.0	0	0.0
CNS Functional Ranks 1–3: (no, moderate, severe dysfunction)	0	0.0	17	43.6	10	37.0	5	55.6
Microcephaly (head circumference <= 3rd percentile)	***1	11.1	2	5.1	5	18.5	3	33.3
Seizure disorder	0	0.0	4	10.3	1	3.7	1	11.1

Linear trend across 4 study groups: MH Chi^2:

*10.7, p 0.001;

**5.1, p 0.02.

***One twin pair had discordant growth Ranks in their 4-Digit Codes (3244-1244). Another pair had discordant CNS structural Ranks (1243–1233) because only one twin presented with microcephaly. Their CNS functional Ranks, however, were both Rank 3. These contrasts in a single component of the 4-Digit Code did not result in discordant FASD diagnostic classifications. Both twin pairs had concordant diagnoses of SE/AE.

#Large contrast in pairwise FASD diagnostic outcomes.

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ADVANCES INPEDIATRIC RESEARCH

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Research Article

Comparison of the 4-Digit Code, Canadian 2015, Australian 2016 and Hoyme 2016 fetal alcohol spectrum disorder diagnostic guidelines

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ABSTRACT

Background: As clinicians strive to achieve consensus worldwide on how best to diagnose fetal alcohol spectrum disorders (FASD), the most recent FASD diagnostic systems show convergence and divergence. Applying these systems to a single clinical population illustrates the contrasts between them, but validation studies are ultimately required to identify the best system.

Methods: The 4-Digit-Code, Hoyme 2016, Canadian 2015 and Australian 2016 FASD diagnostic systems were applied to 1,392 patient records evaluated for FASD at the University of Washington. The diagnostic criteria and tools, the prevalence and concordance of diagnostic outcomes, and validity measures were compared between the systems.

Results: The proportion diagnosed with fetal alcohol syndrome (FAS) and FASD varied significantly (4-Digit-Code 2.1%, ≤79%; Hoyme 6.4%, 44%, Australian 1.8%, 29%; Canadian 1.8%, 16%). Eighty-two percent were diagnosed FASD by at least one system; only 11% by all four systems. Key factors contributing to discordance include: requiring high alcohol exposure; excluding growth deficiency; relaxing the facial criteria; requiring brain criteria that prevent diagnosis of infants/toddlers; and excluding moderate dysfunction from the spectrum. Primate research confirms moderate dysfunction (1-2 domains ≤-2 standard deviations) is the most prevalent outcome caused by PAE (FAS 5%, severe dysfunction 31%, moderate dysfunction 59%). Only the 4-Digit-Code replicated this diagnostic pattern.

Conclusion: The needs of individuals with FASD are best met when diagnostic systems provide accurate, validated diagnoses across the lifespan, the full spectrum of outcome, the full continuum of alcohol exposure; and utilize diagnostic nomenclature that accurately reflects the association between outcome and alcohol exposure.

INTRODUCTION

Alcohol is a well-recognized teratogen and both human and animal research indicates that the impact of prenatal alcohol exposure (PAE) manifests as a spectrum of developmental variations in severity and type of dysfunction across individuals [1-3]. These outcomes vary significantly based on timing and dosage of exposure as well as the presence of other risk factors and are typically characterized as including physical impacts (i.e., growth deficiency, facial dysmorphology and structural brain abnormalities) as well as functional impairment of the central nervous system (CNS). This spectrum of outcome was found in early primate studies on the impact of prenatal alcohol exposure. For example Clarren et al. [4] document the distribution of developmental outcomes when the only risk factor present was PAE. In that study, the primates had been exposed weekly to binge exposures equivalent to a six-pack of beer for the first 3, 6 or entire 24 weeks of gestation (mean maternal peak plasma ethanol concentrations ranged from 176 to 271 mg/dl). The primate model confirmed that PAE causes a spectrum of outcomes; the most common outcome of PAE was moderate CNS dysfunction (the 4-Digit Code equivalent of Neurobehavioral Disorder/Alcohol Exposed ND/AE) (59% of primates) followed

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by more severe CNS impairment (the 4-Digit Code equivalent of Static Encephalopathy/Alcohol Exposed SE/AE) (31%); notably sentinel physical impacts (the 4-Digit Code equivalent of FAS/PFAS) were found in only 5% of primates under these controlled conditions, and a similar number of primates exhibited little to no impacts of PAE (5%).

These facts present a challenge to public health systems seeking ways to best capture this spectrum of outcomes in order to appropriately diagnose and serve individuals that may have been impacted by PAE. As the field of fetal alcohol spectrum disorders (FASD) strives to achieve consensus worldwide on how best to meet this diagnostic challenge, the most recent versions of published guidelines (4-Digit Code, 2004 [5]) Canadian, 2015 [6], Hoyme, 2016 [7], and Australian, 2016 [8] show both convergence and divergence in their approach. For example, the new Canadian and Australian diagnostic systems have many features in common with one another and have adopted the facial criteria of the 4-Digit Code, but diverge substantially from the 4-Digit Code and Hoyme systems by removing growth deficiency from their diagnostic criteria [9] and adopting a nomenclature (FASD with the face, and FASD without the face) that reflects a dichotomy rather than a spectrum of outcomes. The 4-Digit Code [5] and Hoyme [7] criteria continue to generate a spectrum of diagnoses under the umbrella of FASD (fetal alcohol syndrome (FAS), partial FAS (PFAS), Alcohol Related Neurodevelopmental Disorder (ARND), Static Encephalopathy/ Alcohol Exposed (SE/AE), Neurobehavioral Disorder/Alcohol Exposed (ND/AE), and Alcohol Related Birth Defects (ARBD)) and maintain the 3 original core diagnostic criteria (growth deficiency, facial anomalies, and CNS abnormalities). The 4-Digit Code and Hoyme systems differ significantly in their diagnostic nomenclature, diagnostic tools, and the specific criteria used to generate each diagnosis. The Canadian [6] and Hoyme systems require high PAE; the 4-Digit Code and Australian systems require confirmed PAE at any reported level. The Canadian and Australian [8] systems do not include moderate dysfunction under the umbrella of FASD; the 4-Digit Code and Hoyme systems do. The contrasts in these systems create confusion for clinicians faced with diagnosing FASD. Applying these systems to a single clinical population illustrates the contrasts between them, but validation studies are ultimately required to identify the best system.

The objectives of this study were to:

1. Compare the tools, nomenclature and criteria used by the four diagnostic systems.
2. Administer each system to the records of 1,392 patients to:
   a. Compare the prevalence of FASD diagnoses produced by each system.
   b. Assess diagnostic discordance/concordance between the four systems.
   c. Assess and compare the diagnostic performance (validity) of each system.

A comprehensive comparison of the 4-Digit Code and Hoyme 2016 systems was conducted in 2017 [10]. This study expands the comparison to include all four diagnostic systems using the same clinical population of 1,392 patients. Key findings from the published comparison of the 4-Digit Code and Hoyme systems are included in this report, but the Reader is referred to the previous publication [10] for more detail. Since contrasts in the diagnostic tools and criteria used by each system impact our application of each system to our study population, the methods and results for Objective 1 are presented first, followed by the methods and results for Objective 2.

OBJECTIVE 1. COMPARISON OF THE TOOLS, NOMENCLATURE AND CRITERIA USED BY THE FOUR SYSTEMS

Methods

The following tools, nomenclature and criteria used by the four diagnostic systems were compared.

Lip-philtrum guides

The 4-Digit Code introduced two guides: Lip-Philtrum Guide 1 for Caucasians and all races with thinner upper lips like Caucasians, and Lip-Philtrum Guide 2 for African Americans and all races with thicker upper lips like African Americans (Figures 1A and 1B). These Lip-Philtrum Guides were adopted for use by the Canadian and Australian systems. Hoyme 2016 introduced two different lip/philtrum guides: the North American Lip/Philtrum Guide [7] produced from a U.S. white population and the South African Mixed Race Lip/Philtrum Guide [5] produced from a Cape Coloured (mixed race) population in the Western Cape Province (Figures 1C and 1D).

The Rank 1-5 lips depicted on the 4-Digit Code Caucasian and Hoyme et al. [7] North American guides were compared using the objective, quantitative measure of lip thinness called lip circularity (perimeter^2/area) generated by the FAS Facial Photographic Analysis Software [12]. Circularity is computed by outlining the vermilion border of the upper lip with the computer mouse (Figure 2C); the thinner the lip, the bigger the circularity.

PFL normal growth charts

The 4-Digit Code uses the Stromland Scandinavian PFL normal growth charts for all races except African American [13]. The Stromland PFL norms cover the full lifespan (birth to adult). These same charts were used for the Hoyme system. The Canadian and Australian systems use the Stromland charts for patients <6 years of age and the Clarren Canadian PFL [14] charts for patients 6 years of age and older.

Facial analysis software

The 4-Digit Code advises measuring the facial features from 2D digital photos using the FAS Facial Photographic Analysis Software [12]. The Canadian and Australian systems also encourage the use of the FAS Facial Photographic Analysis Software. The authors of the Hoyme system "feel direct examinations of facial features are more practical in an office setting". Since empirical studies have already confirmed the superior accuracy of the photo versus direct method of facial measurement [13,15], a formal assessment of photo versus direct measurement of facial features was not repeated in this study.

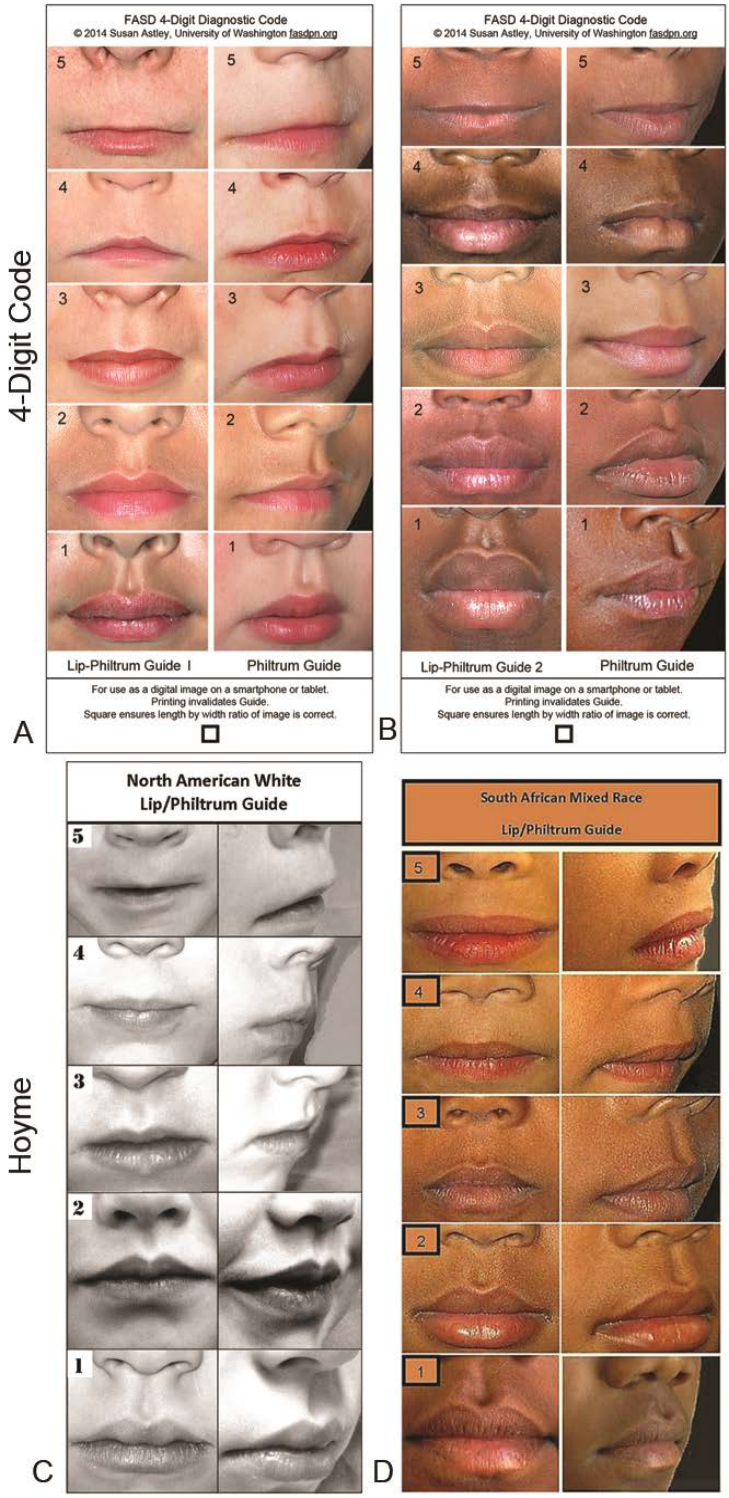


Figure 1. Lip/Philtrum Guides.
The 4-Digit Code [5] introduced two guides in 1999: A) Lip-Philtrum Guide 1 for Caucasians and all races with thinner upper lips like Caucasians, and B) Lip-Philtrum Guide 2 for African Americans and all races with thicker upper lips like African Americans. Hoyme introduced two different lip/philtrum guides: C) the North American Lip/Philtrum Guide in 2016 [7] produced from a U.S. white population (reproduced with permission from Pediatrics [7] copyright 2019 by the AAP) and D) the South African Mixed Race Lip/Philtrum Guide in 2015 [11] produced from a Cape Coloured (mixed race) population in the Western Cape Province (reproduced with permission from AJMG [11] copyright 2019 by John Wiley & Sons).

Diagnostic nomenclature and criteria

Tables were created to illustrate the key contrasts between the diagnoses generated by each system, the nomenclature assigned to each diagnosis, and the diagnostic criteria.

Results

Contrasts in lip-philtrum guides

Astley et al. [10] confirmed the Hoyme lip philtrum guides differ significantly from the 4-Digit Code Lip-Philtrum Guides resulting in substantially relaxed FAS facial features relative to the 4-Digit Code.

The Hoyme 2016 North American White Lip/Philtrum Guide does not match the "Caucasian" 4-Digit Code Lip-Philtrum Guide 1 (Figure 2A).

> **Philtrum:** The Rank 1 through 5 philtrums depicted on both the 4-Digit and Hoyme guides appeared broadly equivalent by visual inspection.
>
> **Upper Lip:** Lip thinness is measured using the objective measure of upper lip thinness (circularity=perimeter^2/area). Circularity confirmed the Hoyme Rank 1, 2, 3, and 4 lips were equivalent to the 4-Digit Ranks 2, 2, 3, and 2 respectively (Figure 2A). The image depicting the vermilion portion of the Hoyme Rank 5 upper lip is not sufficiently clear to judge its level of equivalency with the 4-Digit Code Rank 5 lip. Circularity, as demonstrated in a video link (Figure 2C) confirms the Hoyme Rank 4 lip is substantially thicker than the 4-Digit Code Rank 4 lip (e.g., it is equivalent to the 4-Digit Code Rank 2 lip (Figure 2A). Unlike the 4-Digit Code Lip-Philtrum Guide, the lips pictured on the Hoyme Guide do not become progressively thinner with increasing Rank and no lip on the Hoyme Guide is equivalent to the 4-Digit Ranks 1 or 4. Despite the contrasts between the two lip/philtrum guides, both are intended for use on North American Caucasian populations and thus were used to address Objective 2 below

The Hoyme et al. South African Mixed Race Lip/Philtrum Guide (Figure 1D) does not match the "African American" 4-Digit Code Lip-Philtrum Guide 2 in Figure 1B.

> **Philtrum:** The Rank 1 through 5 philtrums depicted on both guides appeared broadly equivalent by visual inspection.
>
> **Upper Lip:** The objective measure of upper lip thinness (circularity=perimeter^2/area) confirmed the Hoyme Rank 1, 2, 3, 4 and 5 lips were equivalent to the 4-Digit Ranks 2, 3, 3, 3 and 3 respectively (Figure 1 in Astley et al. [10]). Unlike the 4-Digit Code Lip-Philtrum Guide, the lips pictured on the Hoyme Guide do not become progressively thinner with increasing Rank. There are no lip images on the Hoyme Guide that correspond to the 4-Digit Ranks 1, 4 or 5. The Hoyme Rank 5 lip is thicker (circularity 40.1) than the Hoyme Rank 4 lip (circularity 46.0). Most importantly, the Hoyme Rank 4 lip (the clinical cut-off for FAS) is thicker than the 4-Digit Rank 4 lip. The Hoyme Rank 4 lip is equivalent to the 4-Digit Rank 3 lip. The Hoyme Rank 5 lip (circularity 40.1) is substantially thicker than the 4-Digit Rank 5 lip (circularity 80).
>
> Based on our findings here and the findings of Hoyme et al. [11], the South African Mixed Race Lip/Philtrum Guide is not appropriate for use on an African American population and thus was not used to address Study Objective 2. The study population for Objective 2 was adjusted accordingly (as described below) to accommodate this finding

Contrasts in Diagnostic Categories and Nomenclature

The key contrasts in the diagnostic categories and nomenclature used by each system are highlighted in Table 1.

Contrasts in diagnostic criteria

Key contrasts in diagnostic criteria are highlighted in red font in Table 2.

Discussion

Growth deficiency

The Hoyme criteria use the same cut-off (prenatal or postnatal height and/or weight ≤10th percentile) to define growth deficiency as the 4-Digit Code, but the Hoyme criteria classify growth deficiency on a dichotomous scale (present/absent), whereas the 4-Digit Code ranks growth deficiency on a 4-point ordinal scale with emphasis on short stature. The 4-Digit Code method for ranking growth deficiency is confirmed to be highly predictive of CNS dysfunction among individuals with PAE and appears to differentiate growth deficiency (postnatal short stature) significantly associated with PAE from growth deficiency (low birth weight) significantly associated with prenatal tobacco exposure [9]. Rank 3 and Rank 4 growth deficiency was confirmed to be as highly correlated with, and predictive of, severe brain dysfunction as the 4-Digit Code Rank 4 FAS facial phenotype. Individuals with Rank 3 or 4 growth deficiency had a two to three-fold increased risk for severe brain dysfunction. Sixty percent of patients with Rank 4 growth deficiency had severe brain dysfunction. Growth deficiency is so highly predictive of severe CNS dysfunction among infants/toddlers with PAE, it becomes a vital clinical tool for identifying and qualifying infants/toddlers for early intervention. The Canadian and Australian systems removed growth deficiency from their FASD diagnostic guidelines.

Facial phenotype

When compared to the 4-Digit Code Rank 4 FAS facial phenotype (used by the 4-Digit Code, Canadian and Australian systems), the Hoyme FAS facial phenotype is substantially relaxed. This is best illustrated using the 4-Digit Code Facial ABC-Score printed on the backside of the 4-Digit Code "Caucasian" Lip-Philtrum Guide 1 in Figure 3A. The 4-Digit Code Rank 4 FAS facial phenotype is defined by a single ABC-Score (Facial ABC-Score CCC, Face Rank 4) (Figure 3A). The three letters "CCC" reflect the magnitude of expression of the short PFL, smooth philtrum, and thin upper lip in that order. C reflects severe expression in the FAS range, B reflects moderate expression, and A reflects normal expression. The Hoyme FAS facial criteria are relaxed relative to the 4-Digit Code in three ways:

1. Only 2 of 3 cardinal features are required.
2. The PFL is relaxed from the 3rd percentile to the 10th percentile.

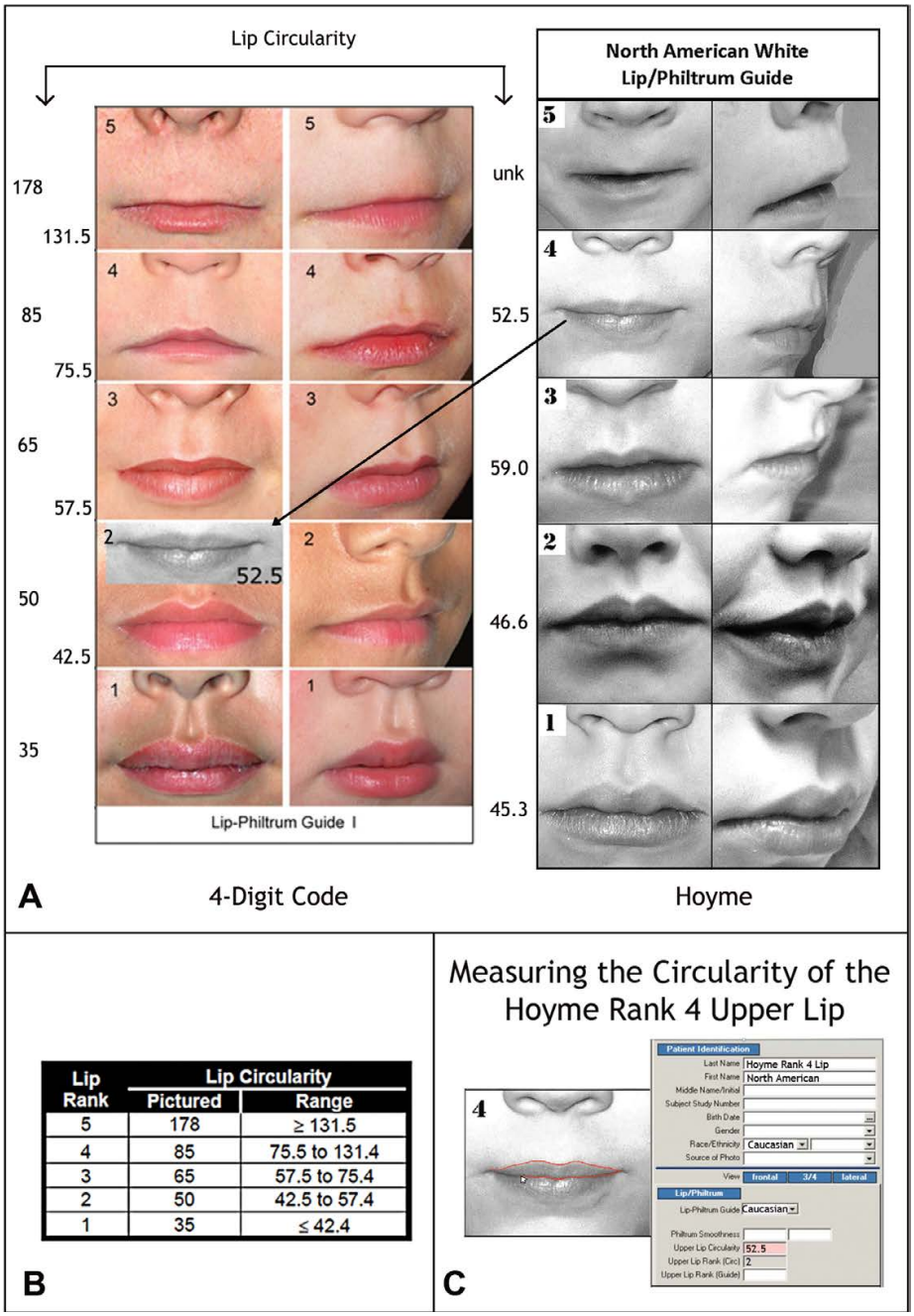


Figure 2. The Hoyme North-American White Lip/Philtrum Guide differs from the 4-Digit Code "Caucasian" Lip-Philtrum Guide 1. The Ranks 1 through 5 philtrums depicted on both Guides appears broadly equivalent, but the upper lips are substantially different. A) Lip circularity (perimeter^2/area) is printed to the left of each guide. B) The range of circularities that define each 4-Digit Code Lip Rank are presented in the Lip Circularity table printed on the backside of the 4-Digit Code Lip-Philtrum Guide. C) The FAS Facial Photographic Analysis Software [12] computes circularity when the User outlines the vermilion border of the upper lip (click on video link for demonstration http://depts.washington.edu/fasdpn/movie/Fig2Cvideo.mp4. Lip circularity confirms the Hoyme Rank 1, 2, 3, and 4 lips are equivalent to the 4-Digit Ranks 2, 2, 3, and 2 respectively. The vermilion portion of the Hoyme Rank 5 upper lip is not sufficiently clear to judge its level of equivalency with the 4-Digit Code Rank 5 lip. There is no lip image on the Hoyme Guide that reflects the 4-Digit Rank 1 or Rank 4 lips. The lips on the 4- Digit Guide become progressively thinner (circularity becomes progressively larger) with increasing Rank. This is not true for the Hoyme Guide. The circularity of the Hoyme Rank 4 lip (the clinical cut-off for FAS) is 52.5, confirming it falls within the circularity range (42.5 to 57.5) of the 4-Digit Code Rank 2 lip. The black and white overlay (A) of the Hoyme Rank 4 lip on the 4-Digit Code Guide 1 demonstrates both visually and numerically that the Hoyme Rank 4 lip is substantially thicker than the 4-Digit Code Rank 4 lip. This analysis confirms the Hoyme North American White Lip/Philtrum Guide is not a valid tool for use with the FASD 4-Digit Diagnostic Code. (North American White Lip/Philtrum Guide used with permission from the American Academy of Pediatrics).

Table 1. Diagnostic categories and overlap of nomenclature used by 4 FASD diagnostic systems.

4-Digit Code 2004 [5]	Hoyme et al., 2016 [7]	Canadian 2015 [6]	Australian 2016 [8]
FAS Alcohol Exposed or Unknown	**FAS** Alcohol Exposed or Unknown	**FASD with the Face** Alcohol Exposed or Unknown	**FASD with the Face** Alcohol Exposed or Unknown
pFAS Alcohol Exposed	**pFAS** Alcohol Exposed or Unknown	**FASD without the Face** High Alcohol Exposure	**FASD without the Face** Alcohol Exposed
SE/AE Static Encephalopathy Alcohol Exposed	**ARND** High Alcohol Exposure Must be ≥ 3 years old		
ND/AE Neurobehavioral Disorder Alcohol Exposed			
	ARBD High Alcohol Exposure		

Table 2. Key contrasts in diagnostic criteria between the four systems.

Criteria	4-Digit Code 2004 [5]	Hoyme et al., 2016 [7]	Canadian 2015 [6]	Australian 2016 [8]
Growth	≤ 10th percentile. Growth: normal, mild, moderate, severe. Emphasis on short stature	≤ 10th percentile Growth: normal/ abnormal	Excluded	Excluded
FAS Face	All 3 features PFL ≤ 3rd percentile. Lip & Philtrum Rank 4 or 5 on 4-Digit Code Lip-Philtrum Guides. Face: normal, mild, mod, severe. Specificity: ~95%. Photo Software confirmed more accurate than direct exam.	2 of 3 features. PFL≤10th percentile. Lip & Philtrum Rank 4 or 5 on Hoyme Lip/Philtrum Guides. Face: normal, abnormal. Specificity: ~71%. "We feel that direct exams are more practical in an office setting"	All 3 features. PFL ≤ 3rd percentile. Lip & Philtrum Rank 4 or 5 on 4-Digit Code Lip-Philtrum Guides. Face: normal, abnormal. Specificity: ~95%. Photo Software recommended.	All 3 features. PFL ≤ 3rd percentile. Lip & Philtrum Rank 4 or 5 on 4-Digit Code Lip-Philtrum Guides. Face: normal, abnormal. Specificity: ~95%. Photo Software recommended.
Alcohol Related Birth defects (ARBD)	Excluded	Cardiac: atrial septal defects, aberrant great vessels, ventricular septal defects, conotruncal heart defects; Skeletal: radioulnar synostosis, vertebral segmentation defects, large joint contractures, scoliosis; Renal: aplastic/ hypoplastic/dysplastic kidneys, "horseshoe" kidneys/ureteral duplications; Eyes: strabismus, ptosis, retinal vascular anomalies, optic nerve hypoplasia; Ears: conductive hearing loss, neurosensory hearing loss	Excluded	Excluded
Brain structure	Structural/neurological abnormalities. OFC ≤ 3rd percentile. Structure alone meets CNS criteria.	Structural/neurological abnormalities. OFC ≤ 10th percentile. Structure alone does not meet CNS criteria.	Structural/neurological abnormalities. OFC ≤ 3rd percentile. Structure alone does not meet CNS criteria. Serves as 1 of 3 brain domains.	Structural/neurological abnormalities. OFC ≤ 3 rd percentile Structure alone does not meet CNS criteria. Serves as 1 of 3 brain domains.
Brain Function	Severe: 3 or more domains ≤ - 2 SDs. Moderate: 1-2 domains ≤ -2 SDs and/or 1 or more domains ≤ 1.5 SDs. Function: normal, moderate, severe.	Moderate to Severe 1 or more domains ≤ -1.5 SDs. Function: normal, abnormal.	Severe: 3 or more domains ≤ -2 SDs. Function: normal, abnormal.	Severe: 3 or more domains ≤ -2 SDs. Function: normal, abnormal.
Alcohol	Confirmed Exposure (at any reported level) or Unknown Exposure (if 4-Digit Rank 4 FAS face present).	Confirmed High Exposure (≥ 6 drinks/wk for (≥ 2 weeks) or ((≥ 3 drinks/occasion, (≥ 2 occasions) or Unknown Exposure (if Hoyme FAS face present).	Confirmed High Exposure (≥ 7 drinks/week) or (≥ 4 drinks/occasion, ≥ 2 occasions) or Unknown Exposure (if 4-Digit Rank 4 FAS face present).	Confirmed Exposure (at any reported level) or Unknown Exposure (if 4-Digit Rank 4 FAS face present).
Children	Diagnostic criteria do not vary with age.	Children ≤ 3 yrs, brain criteria for FAS and PFAS relaxed to developmental delay ≤ -1.5 SDs. Not eligible for a diagnosis of ARND.	Children ≤ 6 yrs: FASD with Face=3 facial features and microcephaly.	Children ≤ 6 yrs: FASD with Face=3 facial features and microcephaly with confirmed or unknown PAE.

At Risk	5.2.1: Prenatal alcohol exposure, with the estimated dose at a level known to be associated with neurodevelopmental effects; Central nervous system criteria from FASD with or without the Face are not met; and there is some indication of neurodevelopmental disorder in combination with a plausible explanation as to why the neurodevelopmental assessment results failed to meet the criteria for substantial impairment (e.g., patient was too young; incomplete assessment). 5.22: All 3 facial features present but do not yet have documentation or evidence of the requisite 3 or more neurodevelopmental domain criteria or true microcephaly. 7.3: Infants and young children with prenatal alcohol exposure but who do not meet the criteria for FASD should be designated as "At risk for neurodevelopmental disorder and FASD, associated with prenatal alcohol exposure."	Individuals who, despite assessment, fail to meet criteria for FASD at the current time, but may nevertheless potentially have FASD. Example include: Neurodevelopmental assessment is incomplete or inconclusive. Despite confirmed PAE, neurodevelopmental impairment is present in fewer than 3 domains. Neurodevelopmental impairment is present in 3 or more domains, but impairment is not sufficiently severe to meet criteria. Comprehensive, age-appropriate neurodevelopmental assessment is impossible or unavailable e.g., in infants and young children. These individuals may be considered 'at risk of FASD' and require follow-up and reassessment. Confirmed or unknown PAE,<6 yrs, all 3 facial features, do not meet neurodevelopmental criteria and do not have microcephaly.

Readers are referred to the published guidelines for each system for how these criteria are used to generate diagnoses under the umbrella of FASD. Key contrasts are in red font.

3. A Rank 4 or 5 thin upper lip is required, but as illustrated in our analysis above, the Rank 4 lip on the Hoyme North American Lip/Philtrum Guide is equivalent to the Rank 2 lip on the 4-Digit Lip-Philtrum Guide 1.

This results in almost every 4-Digit Code Facial ABC-Score meeting the relaxed Hoyme facial criteria (Figure 3B) including 13 of the 15 ABC-Scores that depict the 4-Digit Code Rank 2 (mild) facial phenotype and 3 of the 8 ABC-Scores that depict the complete absence of all three FAS facial features (Rank 1). Clinically, the 4-Digit Code classifies Rank 1 and 2 facial phenotypes as being within the normal range. The practical clinical impact of this relaxation is illustrated in Figure 3C in which an adolescent with high function (e.g., FSIQ 123) and confirmed absence of PAE met the Hoyme criteria for the full FAS facial phenotype.

In addition to the contrasts in facial criteria, the scales of measurement used to clinically classify the facial phenotype also differ. The 4-Digit Code documents the full continuum of expression of the FAS facial phenotype (Face Ranks 1 through 4); a continuum confirmed to be highly predictive of CNS dysfunction [9,16]. Patients with the Rank 3 facial phenotype have a 2-fold increased risk of severe brain dysfunction, whereas patients with the full Rank 4 FAS facial phenotype have a 5-fold increased risk of severe brain dysfunction. In contrast, the Hoyme system documents the facial phenotype as present (equivalent to 4-Digit Face Ranks 2, 3 and 4 and half of Rank 1) and absent (equivalent to the other half of Rank 1) (Figure 3B). The Canadian and Australian systems adopted the 4-Digit Code Rank 4 FAS facial phenotype using the 4-Digit Code Lip-Philtrum Guides, but like the Hoyme et al. system, documents the phenotype as present (4-Digit Code Face Rank 4) or absent (4-Digit Code Face Ranks 1-3). The clinical and research impact of dichotomizing the FAS facial phenotype is illustrated below in Objective 2C.

CNS abnormalities

CNS Functional Abnormalities: The Hoyme criteria that define neurobehavioral impairment appear broadly equivalent to the 4-Digit Code criteria for moderate to severe CNS dysfunction (CNS Ranks 2 and 3). The Canadian and Australian systems adopted the criteria introduced by the 4-Digit Code for severe CNS dysfunction (CNS Rank 3: 3 or more domains of function, 2 or more SDs below the mean). The Canadian and Australian systems exclude moderate dysfunction (the 4-Digit Code equivalent of ND/AE) from under the umbrella of FASD. CNS Structural Abnormalities: The Hoyme criteria for deficient brain growth, abnormal morphogenesis, or abnormal neurophysiology were equivalent to the 4-Digit Code criteria for CNS structural and neurological abnormalities (CNS Rank 4) with the exception of the cut-off used to define microcephaly (Hoyme criteria: ≤10th percentile; 4-Digit Code: ≤3rd percentile). The Canadian and Australian systems adopted the 4-Digit Code criteria for CNS structural abnormalities, but unlike the 4-Digit Code, do not allow structural abnormalities alone to meet the CNS criteria for FASD. Rather, CNS structural abnormalities must be accompanied by at least two domains of function 2 or more SDs below the mean to meet the Canadian and Australian CNS criteria for FASD.

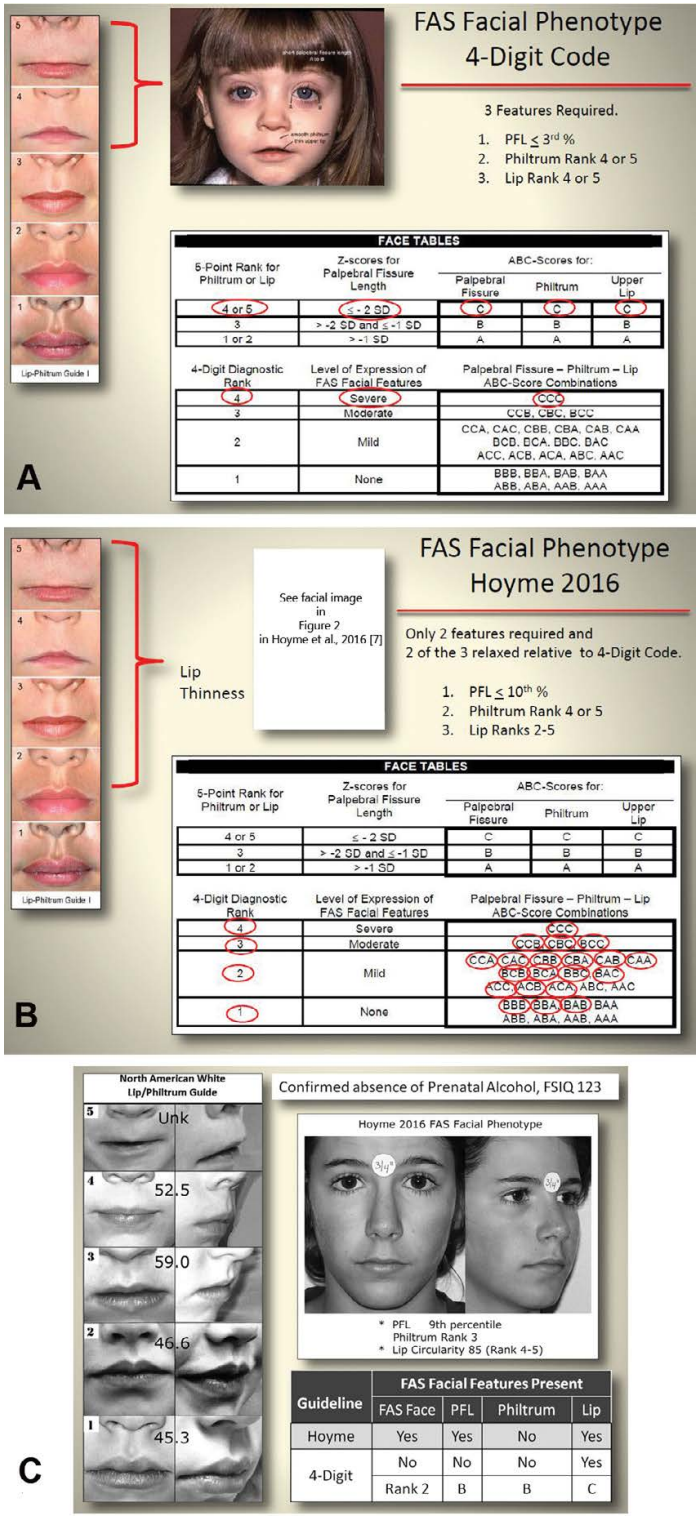


Figure 3. The Hoyme FAS facial phenotype is substantially relaxed relative to the 4-Digit Code.
(A) The 4-Digit Code FAS facial phenotype is defined by the Facial ABC-Score "CCC" as depicted in the Face Table on the backside of Lip-Philtrum Guide 1. (B) The relaxed criteria for the Hoyme FAS facial phenotype results in almost every 4-Digit Code Facial ABC-Score meeting the relaxed Hoyme facial criteria [10]. The prevalence of the FAS facial phenotype was 10-fold higher using the Hoyme criteria (n=552; 40%) compared to the 4-Digit Code (n=54; 4%). (C) The practical clinical impact of this relaxation is illustrated in which an adolescent with high function (e.g., FSIQ 123) and confirmed absence of PAE met the Hoyme criteria for the full FAS facial phenotype. Copyright Susan Astley Hemingway, University of Washington.

Alcohol exposure

The Hoyme 2016 criteria for documented PAE are more stringent than the 4-Digit Code and include thresholds (≥6 drinks/week for ≥2 weeks during pregnancy or ≥3 drinks per occasion on ≥2 occasions during pregnancy). The 4-Digit Code requires a confirmed exposure, but does not set thresholds because: 1) recall and reporting of quantity, frequency, and timing of exposure have been confirmed highly unreliable in a clinical setting (especially in populations like the FASDPN clinic where 85% of patients are not in their birth mother's care at the time of the evaluation); 2) details on quantity, frequency and timing are often unavailable; 3) exposure below a designated threshold has not been confirmed safe for all fetuses [17]; and 4) a recent twin study confirmed risk is not just determined by amount of exposure-fetal genetics modifies risk [18]. The Hoyme system allows FAS and PFAS to be diagnosed when exposure is unknown because the Hoyme FAS facial phenotype is required to be present. The Hoyme FAS facial phenotype, however, is only 71% [19] specific to PAE. The 4-Digit Code allows FAS to be diagnosed when exposure is unknown because FAS requires the presence of the Rank 4 FAS facial phenotype and the Rank 4 face is confirmed to be highly specific (95% specificity) to PAE [20]. The Australian system adopted the alcohol exposure criteria used by the 4-Digit Code. The Canadian system, in contrast, requires high exposure (≥ 7 drinks/week or ≥4 drinks per occasion on ≥2 occasions) when the Rank 4 FAS facial phenotype is absent. In the current study population, of the 1,177 with confirmed PAE, only 46% met the Hoyme or Canadian threshold for high exposure.

OBJECTIVE 2. COMPARISON OF DIAGNOSTIC OUTCOMES ACROSS THE FOUR SYSTEMS

Methods

Study population

The records of 1,392 patients were drawn from 1,522 consecutive patients that received an FASD diagnostic evaluation at the University of Washington Fetal Alcohol Syndrome Diagnostic & Prevention Network (FASDPN). The diagnostic evaluations were performed by interdisciplinary teams between 1993 and 2012 using the FASD 4-Digit Code [5]. The interdisciplinary teams included a medical doctor, psychologist, occupational therapist, speech language pathologist, social worker, family advocate, and public health professional [17,21]. All patients with one or both birth parents African American (130 of the 1,522) were excluded from the study because it was unclear which PFL normal growth chart to use for African Americans when applying the Hoyme system [22] and our findings in Astley et al. [10] and those reported by Hoyme [11] confirm the South African Mixed Race Lip/Philtrum Guide is inappropriate for use on an African American population.

Historically, all records resulting from each patient's FASD diagnostic evaluation have been entered into a research database since 1992 with University of Washington Human Subjects approval and patient consent. Over 95% of patients provide consent for their clinical data to be used for research purposes. Patients' records include the following standardized 4-Digit Code data forms: the New Patient Information Form, the FASD Diagnostic Form, digital facial photos, and the FAS Facial Photographic Analysis Report [5,12]. These data are entered into a research database shortly after the patient's FASD diagnostic evaluation reflecting the tools and growth norms available at that time. Over the decades the 4-Digit Code has evolved (1st edition 1997, 3rd edition 2004) [5,23-25], new tools have been developed like the FAS Facial Photographic Analysis Software (Version 1.0 in 2004, Version 2.1 in 2016) [12], and new more accurate growth norms have been adopted (CDC [26] and WHO [27] growth charts and Stromland Scandinavian PFL charts [28].

For the purposes of research, all patients' clinical 4-Digit Codes are updated to "research" 4-Digit Codes to reflect the most current tools and norms available at the time of the research study. For this study, all 4-Digit Codes were updated to reflect the most current 2004, 3rd edition of the 4-Digit Code [5].

Application of the diagnostic tools and norms

The following tools and norms were used to update the 4-Digit Code FASD diagnoses and generate the Hoyme [7], Canadian [6] and Australian [8] FASD diagnoses

Growth

The Hoyme criteria use the same cut-off (prenatal or postnatal height and/or weight ≤10th percentile) to define growth deficiency as the 4-Digit Code, thus all patients with 4-Digit Code Growth Ranks 2,3 or 4 were classified as meeting the Hoyme growth deficiency criteria.

Height and weight normal growth charts: Height and weight percentiles were generated from the Hall [29] birth weight and length growth charts by gestational age; the World Health Organization (WHO) [27] height and weight growth charts for children 0-2 years of age, and the Centers for Disease Control (CDC) 2000 [26] height and weight growth charts for patients 2 years of age and older. The height percentile was adjusted for mid-parental height [30] when both parents' heights were reported. The Canadian and Australian systems excluded growth deficiency as a criterion for FASD.

Facial features

At the time of each patient's FASD diagnostic evaluation, three standardized, digital facial photographs (Figure 4) were taken and measured using the FAS Facial Photographic Analysis Software [12]. As a result, each patient's research record included the following facial measures: PFLs in millimeters, philtrum smoothness (Rank 1 to 5 on the 4-Digit Code Lip-Philtrum Guide1) and upper lip circularity (perimeter^2/area) and corresponding Lip Rank (Rank 1 to 5 on the 4-Digit Code Lip-Philtrum Guide 1).

Palpebral fissure length: For the 4-Digit Code and Hoyme systems, PFL z-scores were updated to reflect the Stromland Scandinavian PFL growth charts [28]. The Stromland charts are confirmed valid for use on a North American population [13] and address the full age span (birth through adult) represented in our study population. In addition, the Stromland PFL growth charts were generated from digital images, thus meeting the recommendation by Hoyme [7] that PFLs measured from photos should be compared to PFL normal growth charts generated from photos. The Hoyme system cites the Canadian PFL charts [14] as one of several published norms obtained from 2-dimensional photography that one may use, but

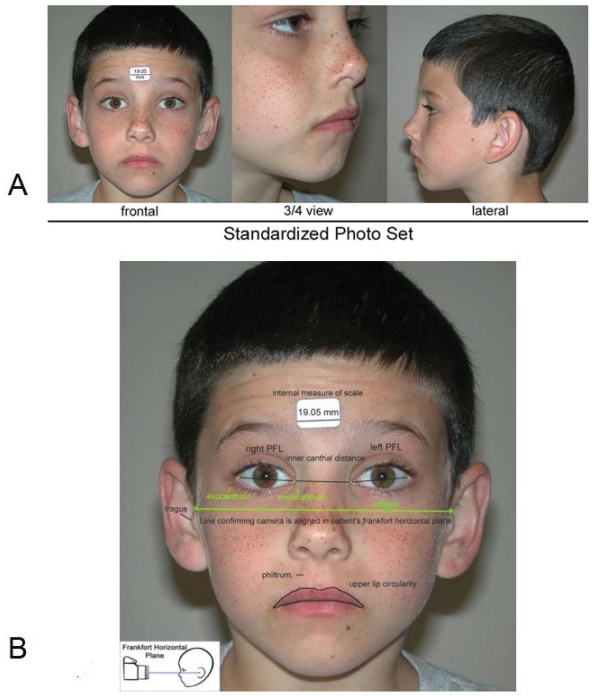


Figure 4. The FAS Facial Photographic Analysis Software [12] was Used to Measure the 3 FAS Facial Features.
A) The palpebral fissure length (PFL), philtrum smoothness, and upper lip thinness are measured from three standardized, digital photographs. B) Standardization includes proper rotation, exposure, focus, and facial expression. An internal measure of scale (a 3/4 inch (19.05 mm) paper sticker) is placed on the forehead to measure the PFLs in millimeters. A video demonstration of the software can be viewed at this link: http://depts.washington.edu/fasdpn/movie/software1024-768cd2.mp4. Copyright Susan Astley Hemingway, University of Washington.

the Canadian norms start at 6 years of age. As demonstrated in Astley et al. [13] transition from the Stromland PFL norms to the Canadian PFL norms at 6 years of age results in an abrupt, artificial decrease in the prevalence of short PFLs due to the discrepancy between the two norms. To avoid this artifact, the Stromland PFL charts that span the entire lifespan were used for the Hoyme system. In accordance with the Canadian and Australian systems, the Canadian PFL growth charts [14] were used for patients 6 years of age and older. The Stromland growth charts [28] were used for patients less than 6 years of age.

Philtrum smoothness and upper lip thinness: The 4-Digit Code "Caucasian" Lip-Philtrum Guide 1 (Figure 1A) was used to Rank philtrum smoothness and upper lip thinness for the 4-Digit Code, Canadian and Australian systems. The Hoyme North American Lip/Philtrum Guide (Figure 1C) was used to rank philtrum smoothness and lip thinness for the Hoyme et al. system. Since the images depicting the Rank 1 through 5 philtrums on the 4-Digit Code and Hoyme guides appeared broadly equivalent (per Objective 1), the philtrum rank assigned at the time of diagnosis using the 4-Digit Code guide was the same philtrum rank assigned to the patient using the Hoyme guide (Figure 1C) (e.g., if the patient had a Rank 4 philtrum using the 4-Digit Code guide, they received a Rank 4 philtrum using the Hoyme guide). In contrast, the analyses in Objective 1 [10] confirmed the Rank 1 through 5 images depicting upper lip thinness did not match between the 4-Digit Guide 1 and the Hoyme North American Guide (Figure 2A). The 4-Digit Code uses the full range of Lip Ranks 1-5 to classify the FAS facial phenotype on a 4-point Likert scale from normal (Face Rank 1) to severe FAS (Face Rank 4). In contrast, the Hoyme FAS/PFAS facial criteria measure lip thinness on a dichotomous scale (thin: ≥ Rank 4, not thin: <Rank 4 on the Hoyme North American Lip/Philtrum Guide (Figure 1C) to classify the FAS/PFAS facial phenotype on a dichotomous scale (present, absent). To accurately and objectively identify which patients met the Hoyme diagnostic criteria for a thin upper lip (≥Rank 4), the Rank 4 upper lip on the Hoyme North American Lip/Philtrum Guide was outlined using the facial software's circularity tool. The video clip in Figure 2C demonstrates this procedure. The circularity of the Hoyme Rank 4 lip was 52.5; equivalent to the 4-Digit Rank 2 lip (defined by the circularity range 42.5 to 57.4). Thus all patients with an upper lip circularity of 52.5 or greater met the Hoyme criteria for a thin upper lip (Rank 4 or 5 on the Hoyme North American Lip/Philtrum Guide).

CNS dysfunction

Based on our findings in Objective 1, all patients with 4-Digit Code CNS Ranks of 2 or 3 (moderate or severe CNS dysfunction) were classified as broadly equivalent to the Hoyme criteria for neurobehavioral impairment (at least 1 domain 1.5 SDs below the mean). All patients with 4-Digit Code CNS Rank 3 (severe dysfunction) were classified as meeting the Canadian and Australian criteria for severe dysfunction (3 or more domains of function, 2 SDs below the mean). All patients with 2 domains of severe dysfunction and microcephaly (OFC≤3rd percentile) also met the Canadian and Australian criteria for severe dysfunction.

CNS structural abnormalities

Based on our findings in Objective 1, all patients with a 4-Digit Code CNS Rank4 (structural/neurological abnormalities) were classified as meeting the Hoyme criteria for deficient brain growth, abnormal morphogenesis, or abnormal neurophysiology. In addition, all patients with an OFC ≤10th percentile were classified as meeting the Hoyme CNS structural criteria. All patients with a 4-Digit Code CNS Rank 4 (structural/neurological abnormalities) were classified as meeting the Canadian criteria for impairment in neuroanatomy or neurophysiology and the Australian criteria for abnormal brain structure/neurology. In contrast to the Hoyme et al. system, the 4-Digit Code, Canadian and Australian systems use a cut-off of ≤3rd percentile for microcephaly. The WHO [27] OFC charts for children 0-5 years of age and the Nellhaus [31] OFC growth charts for children 5-18 years of age were used for all four systems

Statistical analyses

Descriptive statistics (valid percentages) were used to profile the study population. Chi-square tests were used to compare groups and linear trends across groups for outcomes measured on nominal or ordinal scales. One-way analysis of variance (ANOVA) was used to compare means and detect linear trends across three or more groups when outcomes were measured on a continuous scale. T-tests were used to compare means between two independent groups.

Various measures of performance (validity) were administered

to each system to address Objective 2C. Validity is the degree to which a tool (or diagnostic system) is measuring what it purports to measure. Validity is not determined by a single statistic, but by a body of research that demonstrates the relationship between the diagnostic system and the condition it is intended to measure. There are three overarching forms of validity: content validity, criterion validity, and construct validity. Content Validity is a measure of how well the items in the diagnostic system represent the entire range of possible items the diagnostic system should cover. Criterion validity is a measure of a diagnostic tool's accuracy relative to a gold standard. Construct validity refers to the degree to which a test measures what it claims, or purports, to be measuring. It refers to the ability of a measurement tool to measure the physiological concept being assessed. Convergent and discriminant validity are two subtypes of construct validity. Convergent validity refers to the degree to which two measures of constructs that theoretically should be related are in fact related. In contrast, discriminant validity tests whether concepts or measurements that are supposed to be unrelated are in fact unrelated. An important aspect of clinical research is the inference that an association represents a cause-effect relationship. Features of associations that support causation include: the strength of the association; the consistency of observed evidence; specificity of the relationship; temporality of the relationship; the biological gradient of dose-response, biological plausibility; and experimental confirmation. Predictive validity refers to a tool's ability to predict something it should theoretically be able to predict. Statistical measures used to assess these constructs include linear correlation coefficients and tests for trends. Fundamental measures of diagnostic accuracy include sensitivity and specificity. The sensitivity of a test is the proportion of people with the condition who test positive for it (the true positive rate). The specificity of a test is the proportion of people who do not have the condition who test negative for it (the true-negative rate).

Results

Study population

The clinical and socio-demographic profile of the study population (N=1,392) is presented in Table 3. The population spanned the entire age range from newborn to adult with 57% Caucasian and 44% female. Eighty-five percent had confirmed PAE; 15% had unknown PAE. Patients with unknown PAE were included because all four diagnostic systems allow a diagnosis of FAS when PAE is unknown. Since the publication of the 2017 study comparing the 4-Digit Code to the Hoyme system [10], updated information became available on 2 of the 1,392 patients, impacting the distribution of diagnoses generated by the two systems by a fraction of a percent in this study relative to the 2017 study.

Objective 2a: Compare the prevalence of FASD diagnostic outcomes generated by the four systems

The distribution of diagnoses varied substantially across the 4 systems as illustrated in Table 4 and Figures 5A and 5B.

The proportion of patients diagnosed with FAS and FASD varied significantly across the systems (4-Digit 2.1% and ≤79%; Australian 1.8% and 29%; Canadian 1.8% and 16%; and Hoyme 6.4% and 44% (Figure 5A). Even though the proportion of patients diagnosed with FAS (1.8%-2.1%) by the 4-Digit, Canadian and Australian systems was comparable, the patients that made up the 2% within each system were different (see Objective 2b). The distribution of diagnoses also varied substantially across the four systems among the subset of patients <6 years of age at the time of diagnosis (Figure 5B). Key factors contributing to the diagnostic variability include:

1) The Canadian and Australian systems exclude moderate dysfunction as an outcome caused by PAE. This resulted in the greatest magnitude of diagnostic variability between the 4 systems. Exclusion of moderate dysfunction prevented a Canadian diagnosis of FASD in 666 patients with moderate dysfunction and confirmed PAE (48% of whom had confirmed high PAE). 76% had 1 or 2 (but not 3) domains of severe dysfunction and all had multiple domains of moderate dysfunction. Exclusion of moderate dysfunction prevented an Australian diagnosis of FASD in 642 patients with moderate dysfunction and confirmed PAE (50% of whom had confirmed high PAE). 74% had 1 or 2 (but not 3) domains of severe dysfunction and all had multiple domains of moderate dysfunction. Primate research confirms moderate dysfunction (ND/AE) is the most prevalent outcome caused by PAE (5% FAS/PFAS, 31% SE/AE; 59% ND/AE, 5% not FASD) (Figure 6). Only the 4-Digit Code replicated this distribution of diagnoses observed in the primate model of FASD as discussed more fully below. Fifty-three percent of the 1,177 patients with confirmed PAE received a diagnosis of ND/AE using the 4-Digit Code (65% were over 6 years of age).
2) The Canadian and Hoyme systems require confirmed high exposure to alcohol in the absence of the FAS facial phenotype. This prevented 47% of 1,155 patients with confirmed PAE, but without the FAS facial phenotype from receiving a FASD diagnosis using the Canadian system. Forty-three percent of these 548 patients had 1 to 2 domains of severe dysfunction; 34% had 3 or more domains of severe dysfunction. The requirement for high PAE also prevented 59% of 664 patients with confirmed PAE, but without the Hoyme FAS facial phenotype, from receiving a FASD diagnosis using the Hoyme system. Forty-two percent of these 389 patients had 1 to 2 domains of severe dysfunction; 33% had 3 or more domains of severe dysfunction. For reference, the proportion of patients with confirmed high PAE (Alcohol Rank 4) within each FASD diagnosis rendered by the 4-Digit Code is marked by yellow lines (Figures 5A and 5B).
3) The Australian and Canadian systems excluded growth deficiency as a criterion for FASD. This prevented the early identification of 70% of children <8 years old with confirmed PAE and growth deficiency as especially high risk for severe brain dysfunction (3 or more domains of function 2 or more SDs below the mean) later in childhood [9]. More specifically, of the 770 patients classified as Not FASD by the Australian system, 559 had confirmed PAE. Of the 559 with confirmed PAE, 221 were under 8 years of age and 69 presented with Growth Rank 2, 3 or 4 (height and/or weight at or below the 10th percentile). Seventy-percent of these children with confirmed PAE and growth deficiency will present with severe CNS dysfunction later

Table 3. Sociodemographic and 4-Digit Code clinical profile of the study population (n=1,392).

Characteristic	N	Valid %
Gender		
female	608	44
male	784	56
Race/ethnicity		
Caucasian	788	57
Native American	126	9
Hispanic	37	3
African American	0	0
Other (including mixed race)	434	31
Age at FASD diagnostic evaluation (years)		
0-2	141	10
3-5	314	23
6-7	234	16
8-12	411	30
13-19	241	17
20-49	51	4
4-Digit Code Diagnoses (and Categories)		
FAS/AE or A? (A,B)	29	2
PFAS/AE (C)	53	4
SE/AE (E,F)	388	28
ND/AE (G,H)	624	45
SPF/AE (I)	22	1
Normal/AE (J)	69	5
Not FASD/A? (D, K-V)	207	15
Growth Rank		
Normal (height & weight > 10th percentile): 1	954	68
Mild (height and/or weight≤10th but both > 3rd percentile): 2	176	13
Moderate: (height or weight≤3rd percentile): 3	161	12
Severe (height & weight≤3rd percentile): 4	101	7
Face Rank		
Normal (no features): 1	705	51
Mild (1-2 features): 2	530	38
Moderate (2.5 features): 3	103	7
Severe (all 3 features): 4	54	4
CNS Rank		
No structural/functional abnormalities: 1	109	8
Moderate dysfunction (1-2 domains ≤ -2 SDs): 2	739	53
Severe dysfunction (3 or more domains ≤ -2 SDs): 3	307	22
Severe structural/neurological abnormalities: 4	237	17
CNS Functional Rank*		
No dysfunction: 1	171	12
Moderate dysfunction: 2	829	60
Severe dysfunction: 3	392	28
Alcohol Rank		
Prenatal Alcohol Exposure (PAE) confirmed absent: 1	0	0
PAE Unknown: 2	215	15
PAE confirmed: :Level unknown: 3	198	14
PAE confirmed: :Level reported moderate: 3	353	26
PAE confirmed: Level reported high: 4	626	45

* Includes all 1,392 subjects including the 236 with CNS Rank 4 structural/neurological abnormalities. Abbreviations: AE: alcohol exposed; A?: alcohol exposure unknown; ND neurobehavioral disorder; SD standard deviations; SE static encephalopathy; SPF sentinel physical features

in childhood when they are old enough to participate in a comprehensive neuropsychological assessment. None were identified as "At Risk" by the Australian system. Of the 822 children classified as Not FASD by the Canadian system, 611 had confirmed PAE. Of the 611 with confirmed PAE, 176 were under 8 years of age and 48 presented with Growth Rank 2, 3 or 4. Seventy-one percent of these children with confirmed PAE and growth deficiency will present with severe CNS dysfunction after the age of 8 years. None were identified as "At Risk" by the Canadian system.

4) Relaxation of the FAS facial criteria by the Hoyme system (Figure 3), resulted in ten times more patients presenting with the "Hoyme FAS facial phenotype" (552, 40%) than the Rank 4 FAS facial phenotype (54, 4%) used by the 4-Digit Code, Canadian and Australian systems [10]. Seventy-one percent of the 552 patients with the Hoyme FAS facial phenotype had 4-Digit Code Face Ranks 1 and 2. The relaxed Hoyme criteria also resulted in a clinically significant reduction in facial specificity (71% to 75%) [19,32] to alcohol relative to the Rank 4 FAS facial phenotype (>95% specificity) [10]. Of the 552 patients with the Hoyme FAS facial phenotype, almost half (43%) did not receive a diagnosis under the umbrella of FASD using the Hoyme system. In contrast, all 54 patients with the 4-Digit Code Rank 4 FAS face met criteria for a diagnosis under the umbrella of FASD using the 4-Digit Code. More details on these outcomes are presented in Astley et al. [10].

5) Switching from the Stromland PFL growth charts to the Clarren PFL growth charts at 6 years of age, as recommended by the Canadian and Australian systems, can result in the FAS facial phenotype appearing to "disappear" at age 6 years. Although the Stromland PFL growth charts [28] span the entire age range from birth to adult, the Canadian and Australian systems recommend use of the Clarren PFL normal growth charts [14] that start at age 6 years and the Stromland PFL charts for children under 6 years of age. This results in an artificial decrease in the prevalence of short PFLs and the FAS facial phenotype in children >6 years of age because the mean PFL for age in the Clarren charts is roughly half a SD larger than the PFL in the Stromland charts in Figure 2 in [13]. A PFL of 23 mm in a 6 year old boy is -2.1 SDs on the Stromland charts, but -1.6 SDs on the Clarren charts. To illustrate the impact this has on diagnostic outcomes, of the 30 patients >6 years of age with the Rank 4 FAS facial phenotype using the Stromland PFL charts, only 21 met the Rank 4 FAS facial phenotype criteria using the Clarren PFL charts. This is a 30% reduction in prevalence of the FAS facial phenotype. The discrepancy between the two charts will also result in the FAS facial phenotype appearing to "disappear" with age. If a child presents with the FAS facial phenotype using the Stromland charts at age 5 years, the child will appear to lose the FAS facial phenotype upon re-evaluation at 6 years of age as a result of switching to the Clarren PFL charts. The 4-Digit Code recommends use of the Stromland PFL

Table 4. Prevalence and concordance of FASD diagnoses across the four diagnostic systems.

Variables	Diagnoses generated by the four systems and the various names applied to each													
	FAS, FASD/with Face		PFAS		SE/AE, ARND-severe*, FASD/no Face		ND/AE, ARND-moderate**		ARBD		"FASD" FASD		Not FASD (includes At-Risk)	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Number diagnosed by each system														
4 Digit	29	2.1	53	3.8	388	27.9	624	44.8			1094	78.6	299	21.4
Australian	25	1.8			372	26.7					397	28.5	995	71.5
Canada	25	1.8			201	14.4					226	16.2	1166	83.8
Hoyme	89	6.4	207	14.9	69	5.0	192	13.8	56	4	613	44	779	56.0
Number diagnosed by at least 1 system														
	107	7.7	241	17.3	430	30.9	624	44.8	56	4	1138	81.8	1240	89.0
Number diagnosed by all 4 systems														
	12	0.9	19	1.4	53	3.8	0	0	0	0	152	10.9	235	16.9

* ARND-severe: patients with 3 or more functional domains -2 SDs below the mean. ** ARND-moderate: patients with 2 or more functional domains -1.5 SDs below the mean, but less than 3 functional domains -2 SDs below the mean. "FASD": 4-Digit Code includes FAS and PFAS under the FASD umbrella, but notes SE/AE and ND/AE are only FASDs if a patient's prenatal alcohol exposure caused their SE or ND.

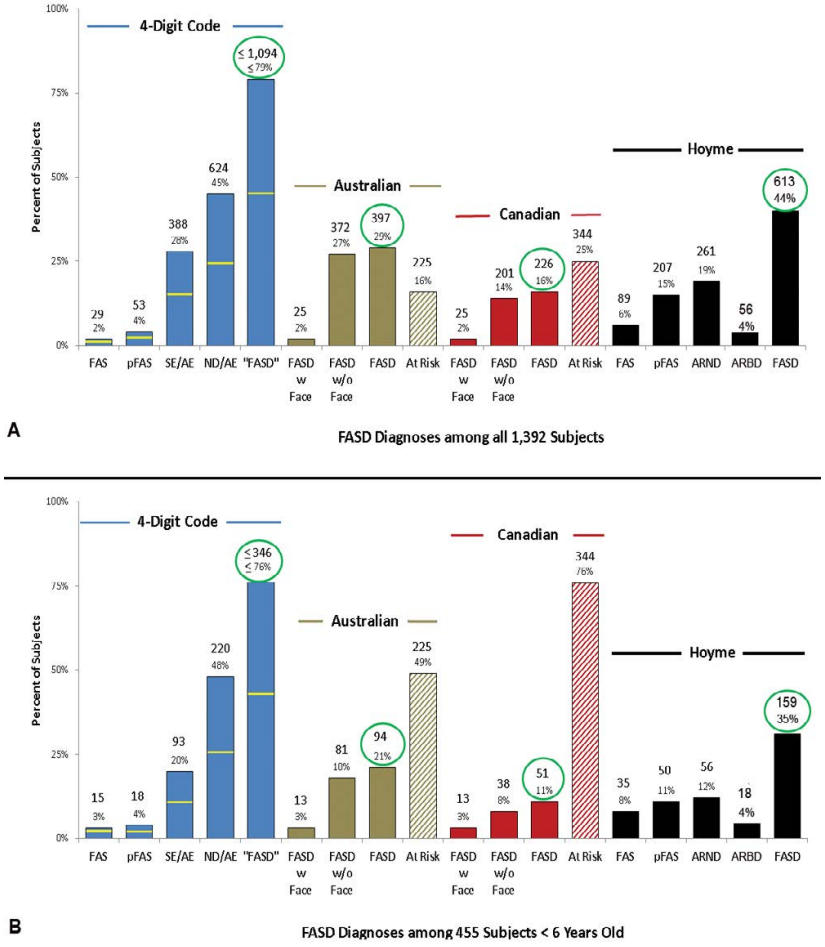


Figure 5. FASD diagnostic outcomes are compared across the four FASD diagnostic systems.
(A) Diagnoses across the entire population (n=1,392). (B) Diagnoses across the subset of 455 patients less than 6 years of age at the time of diagnosis. The yellow lines on the blue bars reflect the proportion of patients with confirmed high PAE (4-Digit Code Alcohol Rank 4). The bars labeled FASD for each system reflect the total number of patients diagnosed under the umbrella of FASD by each system. The term "FASD" is in quotes for the 4-Digit Code to denote that the 4-Digit Code defines FASD as including FAS, PFAS and only those individuals whose SE or ND was caused (at least in part) by their prenatal alcohol exposure.

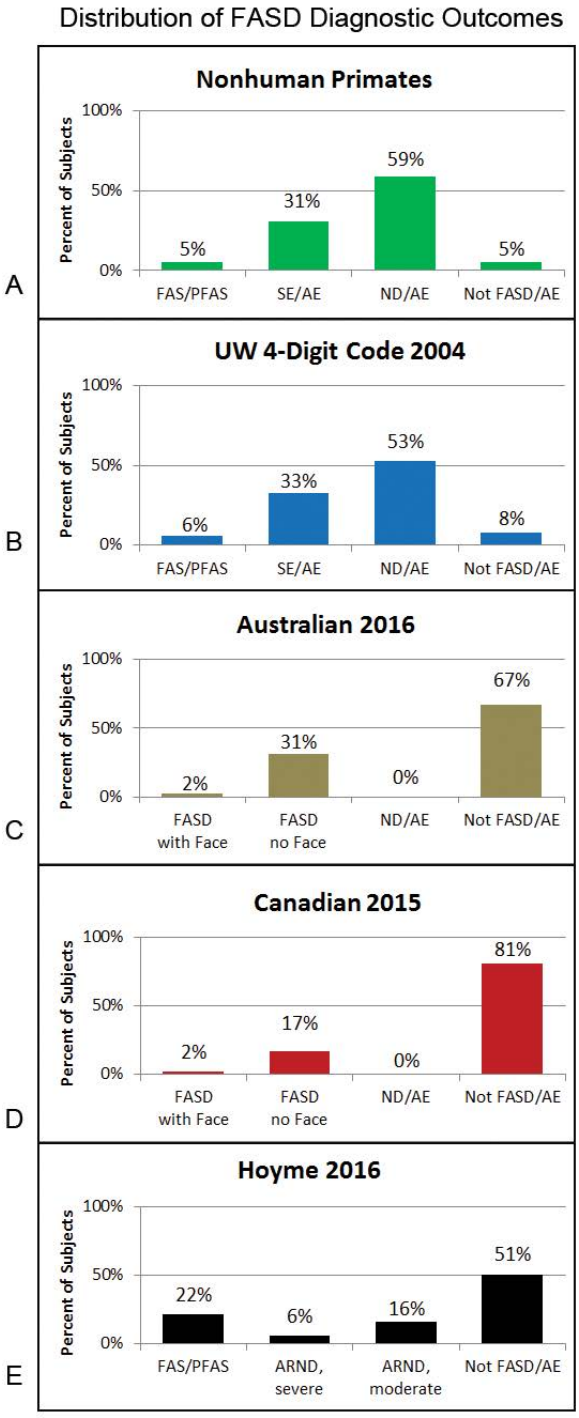


Figure 6. Nonhuman-primate study confirms moderate dysfunction is the most prevalent outcome under the umbrella of FASD.
(A) The 4-Digit Code was applied to the outcomes observed in our highly controlled primate model of FASD [4] where PAE was the only risk factor. Moderate dysfunction (ND/AE) was the most prevalent outcome (59%). (B) The 4-Digit Code was the only diagnostic system that replicated the distribution of diagnoses observed in the primate model. (C-D) The Australian and Canadian systems omit moderate dysfunction from FASD. B-E) The bar charts reflect the distribution of diagnostic outcomes across the 4 systems among the 1,177 patients with confirmed PAE.

Abbreviations: AE: Alcohol Exposed; ARND: Alcohol Related Neurodevelopmental disorder; ND: Neurobehavioral Disorder; SE: Static Encephalopathy. ARND-severe reflect the subset of patients meeting the Hoyme ARND criteria that have 3 or more domains of function≤2 SDs below the mean (rendering it comparable to SE/AE and FASD/no Face. ARND-moderate is the remainder of patients meeting the Hoyme ARND criteria that have less than 3 domains≤2 SDs below the mean.

charts across the full age span [13] to avoid these artifacts in measurement.

6) The Hoyme system includes Alcohol Related Birth Defects (ARBD/AE) under the umbrella of FASD; the other systems do not. Fifty-six individuals met the Hoyme criteria for ARBD/AE (Figure 5A). Of the list of defects that meet the Hoyme criteria for ARBD/AE (Table 2), four types of defects were observed among the 276 patients who met the Hoyme alcohol criteria, but did not meet the Hoyme criteria for FAS, PFAS or ARND. The number of patients presenting with each feature was as follows: strabismus (5), ptosis (36) cardiac anomalies (12) and scoliosis (8). Seven of the 56 patients presented with two of these features. The reported prevalence of these features across the entire study population of 1,392 patients was ptosis (9.0%), cardiac anomalies (3.9%), strabismus (0.5%) and scoliosis (0.4%). Cardiac anomalies were significantly more prevalent among patients receiving a FASD diagnosis (6.5%) using the Hoyme system than among those not receiving a FASD diagnosis (1.9%) (Chi^2 19.2, p=0.000). Ptosis was also significantly more prevalent among patients receiving a FASD diagnosis (14.4%) using the Hoyme system than among those not receiving a FASD diagnosis (4.6%) (Chi^2 38.7, p=0.000). Cardiac anomalies and ptosis were also significantly more prevalent among patients with FASD than without FASD when the other three systems (4-Digit Code, Australian and Canadian) were used to generate the FASD diagnoses. None of these anomalies were significantly correlated with any measure of PAE available in the FASDPN dataset.

Objective 2b: Assess diagnostic discordance/concordance between the four systems

Very little diagnostic concordance was observed across all four diagnostic systems. Of the 1,392 patients, 1,138 (82%) were diagnosed with FASD by at least one of the four systems (Table 4). In contrast, only 152 (11%) were diagnosed with FASD by all four systems. Of the 107 (8%) diagnosed with FAS by at least one of the 4 systems, only 12 (1%) were diagnosed FAS by all four systems.

The patient-by-patient diagnostic outcomes generated by the 4-Digit Code were compared directly with the diagnoses generated by the Hoyme (Figure 7) Canadian (Figure 8) and Australian (Figure 9) systems. The Canadian system was also compared directly with the Australian system (Figure 10) and the Hoyme system in (Figure 11). Of the 1,392 patients, concordant diagnoses (including those being classified as "Not FASD") were as follows: 4-Digit vs Canadian: 31%; 4-Digit vs Hoyme: (38%); 4-Digit vs Australian: (45%); Canadian vs Hoyme (39%) and Canadian vs Australian: (82%). The higher level of concordance between the Canadian and Australian systems is due to the fact that the Australian system adopted the criteria used by the Canadian system, with one important exception. The Canadian system requires confirmed high PAE. The Australian system requires confirmed PAE at any reported level. The higher

level of concordance between the Canadian and Australian systems was due largely to the high proportion (66%, 918/1,392) of patients classified as not under the umbrella of FASD ("At Risk" and "Not FASD").

The discordance across the systems ranged from subtle differences (e.g., the patient received a diagnosis of FAS by one system and PFAS by another system) to marked contrasts (e.g., the patient received a diagnosis of FAS by one system and no diagnosis under the umbrella of FASD by another system). A few examples of these marked contrasts include the following. Additional contrasts are presented in the legends for Figures 7-11.

1. Of the 21 patients that received a diagnosis of FAS/Alcohol Exposed using the 4-Digit Code, 7 had FASD ruled-out altogether using the Hoyme system (see the 4-Digit Code FAS/AE column in Figure 7). All 7 patients were less than 5 years of age. They presented with CNS structural abnormalities (e.g., microcephaly: OFC≤3rd percentile), but early development was broadly within the normal range. All 7 were too young to engage in the necessary level of testing to accurately rule-out moderate or severe CNS dysfunction. The Hoyme system requires both CNS structural abnormalities (e.g., OFC≤10th percentile) and evidence of moderate to severe CNS dysfunction for a diagnosis of FAS.
2. Among the 207 patients that were classified "Not FASD" by the 4-Digit Code, 15 received a FAS diagnosis and 23 received a PFAS diagnosis using the Hoyme system (Figure 7). The 4-Digit Code does not render a diagnosis under the umbrella of FASD if: 1) alcohol exposure is unknown and 2) the Rank 4 FAS facial phenotype is absent. If an individual does not have a confirmed PAE, the 4-Digit Code Rank 4 FAS face can serve as confirmation of exposure because the phenotype is confirmed to be so highly specific to (caused only by) PAE (> 95% specificity) [17]. The Hoyme system allowed these 38 patients with unknown alcohol exposures to receive a diagnosis of FAS or PFAS because they presented with the Hoyme FAS face. But the Hoyme FAS facial criteria are so relaxed (specificity 71% to 75% [19,32]), the facial phenotype does not provide the necessary level of specificity to alcohol to use the facial phenotype to confirm exposure. Among the 38 individuals with unknown PAE and a Hoyme diagnosis of FAS or PFAS, 18 had relaxed PFLs (4th-10th percentile), 16 had relaxed philtrums (4-Digit Philtrum Ranks 2 and 3), 22 had relaxed lips (4-Digit Lip Ranks 1-3); 4 had no FAS facial features (4-Digit Face Rank 1); and 19 had only 1 FAS facial feature (4-Digit Face Rank 2).
3. Among the 779 patients that were classified "Not FASD" using the Hoyme system, 24 received a FAS/PFAS diagnosis using the 4-Digit Code (Figure 7, red bars in the Hoyme "Not FASD" row). All 24 presented with the Hoyme FAS face, but none met the Hoyme FAS or PFAS diagnostic criteria. The Hoyme FAS criteria require the presence of both CNS structural abnormalities (e.g., OFC≤10th percentile) and neurobehavioral impairment. Fifteen presented with a small head circumference (OFC≤10th percentile), but did not present with neurobehavioral impairment. All 15 were under 6 years of age. Of the 15 infants/toddlers, all were microcephalic (OFC≤3rd percentile), but did not present with developmental delay >1.5 SD below the mean. Nine of the 24 presented with severe CNS dysfunction, but were normocephalic. Of the 22 with confirmed PAE, 7 had levels that were reportedly too low to meet the Hoyme alcohol exposure criteria.
4. Among 82 patients diagnosed FAS/PFAS by the 4-Digit Code, 21 were classified as "Not FASD" by the Canadian system (Figure 8). Of the 4 with FAS/Alcohol unknown, all were > 6 years of age with microcephaly, but 2 with severe CNS dysfunction did not meet the Canadian FAS face criteria (the PFLs were -1.7 SDs on the Clarren PFL charts [14] used by the Canadian system, compared to -2.5 SDs on the Stromland PFL charts [28] used by the 4-Digit Code). The other 2 patients met the Canadian facial criteria, but did not meet the severe CNS criteria, despite their microcephaly. Of the 17 with PFAS/AE, all had Rank 3 facial phenotypes (classified as "normal" by the Canadian system) and 14 had Rank 3 alcohol exposure (not meeting the high PAE required by the Canadian system). The remaining 3 had high PAE and microcephaly, but did not meet the Canadian requirement for severe CNS dysfunction.
5. Among 624 patients diagnosed ND/AE by the 4-Digit Code, 220 received an "At Risk" classification, and 404 received a "Not FASD" classification by both the Australian (Figure 9) and Canadian (Figure 8) diagnostic systems. The 404 patients classified "not FASD" by the two systems were all >6 years of age with confirmed PAE (half with confirmed high PAE). Eighty-seven percent had 1 or 2 (but not 3) domains of severe dysfunction and all had multiple domains of moderate dysfunction. The Australian and Canadian systems do not classify patients with moderate dysfunction under the umbrella of FASD. Primate research documents moderate dysfunction is the most prevalent outcome (59%) caused by prenatal alcohol exposure (Figure 6A).
6. Among the 372 patients diagnosed "FASD without the Face" by the Australian system, only 201 (54%) received the same diagnosis from the Canadian system (Figure 10). The remaining 46% (42+129) had confirmed PAE, but did not receive a FASD diagnosis by the Canadian system because they did not meet the Canadian requirement for high PAE.

Objective 2c: Assess measures of performance (validation)

Validity is the degree to which a tool (or diagnostic system) is measuring what it purports to measure. Space does not permit a comprehensive assessment of performance across all 4 systems. Below are select examples to demonstrate the impact different measurement scales and criteria can have on the clinical and research performance of the diagnostic systems. The Reader is referred to Astley [17] for a comprehensive assessment of validation of the 4-Digit Code.

Correlation between the FAS Facial Phenotype and Prenatal Alcohol Exposure

All four systems allow a diagnosis of FAS to be made in the absence of confirmed PAE because the FAS facial phenotype is so highly specific to (caused only by) PAE, the required presence of the face serves as confirmation of PAE. For this practice to be medically valid, the FAS facial phenotype has to be highly specific to PAE. The

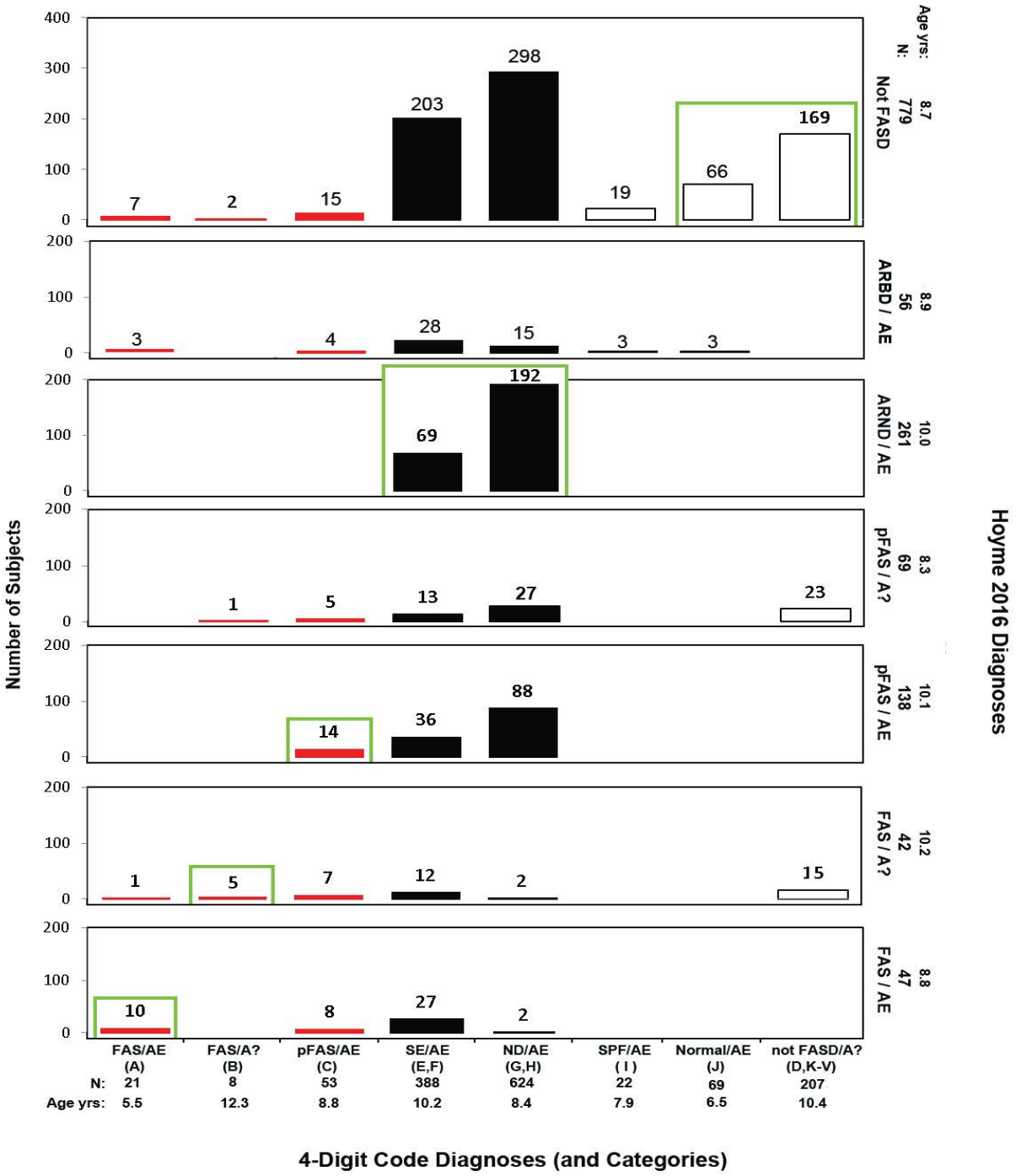


Figure 7. Cross-tabulation of the 4-Digit Code and Hoyme 2016 FASD Diagnostic Outcomes.
Diagnostic concordance (green boxes) between the 4-Digit Code and Hoyme 2016 systems was observed in 38% (528/1,392) of the patients. Red bars reflect FAS and PFAS diagnoses using the 4-Digit Code. Black bars reflect the rest of the FASD spectrum using the 4-Digit Code. As a demonstration for how to interpret this figure; 21 patients received a 4-Digit Code Diagnosis of FAS/AE. Of the 21 patients, 10 received a FAS/AE diagnosis, 1 received a FAS/A? and 10 did not receive a diagnosis under the umbrella using the Hoyme 2016 diagnostic system.
Abbreviations: 4-Digit Code Categories A-V are case-defined in the Diagnostic Guide for FASD [5]. AE: alcohol exposed; A?: alcohol exposure unknown; ND: neurodevelopmental disorder; Not FASD/A?: Individuals who present with or without growth, facial, and/or CNS abnormalities, but are not under the umbrella of FASD because their prenatal alcohol exposure is unknown and they do not meet the criteria for FAS/A?. SE: static encephalopathy; SPF: Sentinel Physical Findings, individuals who present with growth deficiency and/or 1 to 3 FAS facial features, but have normal CNS structure and function; Normal: no evidence of growth, facial, or CNS structural/functional abnormalities. Age yrs; mean age in years at diagnosis.

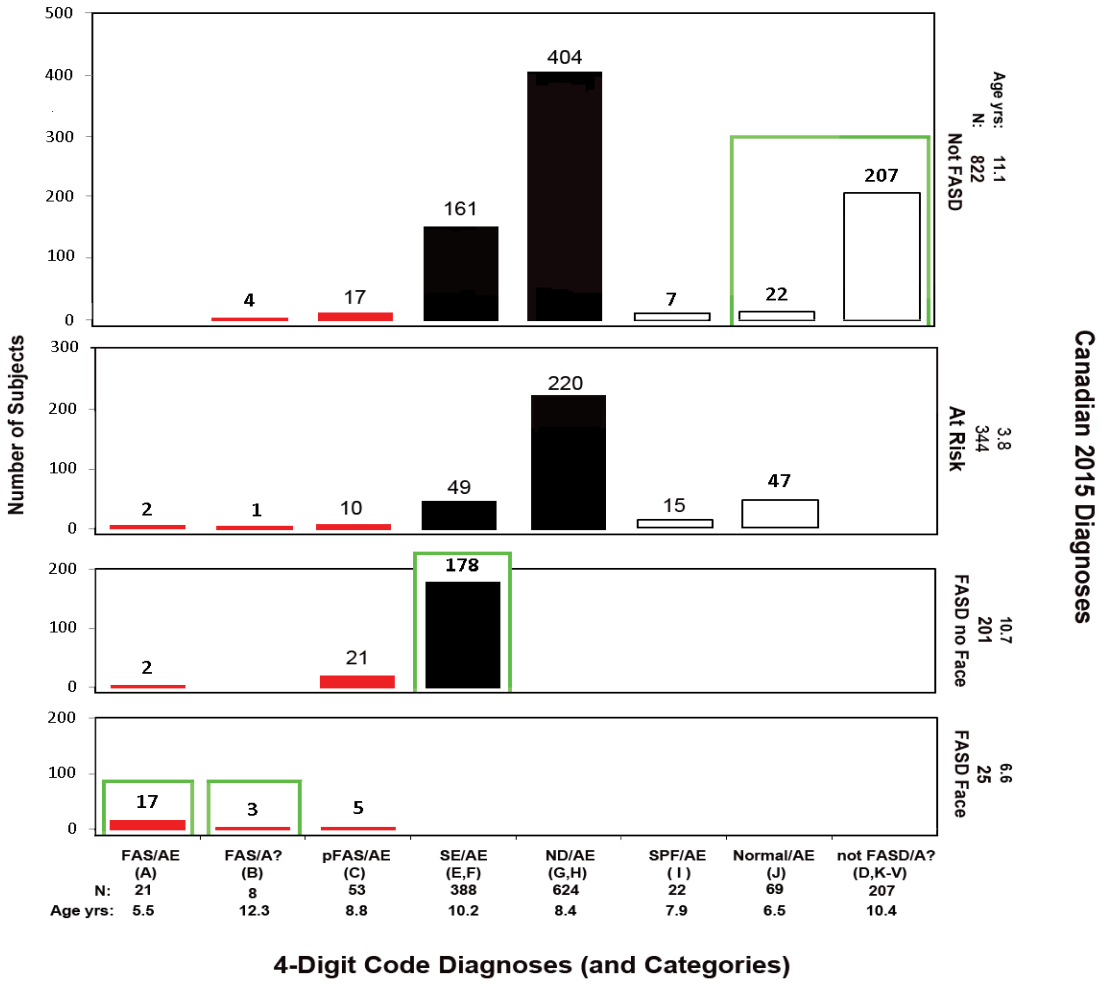


Figure 8. Cross-tabulation of the 4-Digit Code and Canadian 2015 FASD Diagnostic Outcomes.
Diagnostic concordance (green boxes) between the 4-Digit Code and Canadian 2015 systems was observed in 31% (427/1,392) of the patients. Red bars reflect FAS and PFAS diagnoses using the 4-Digit Code. Black bars reflect the rest of the FASD spectrum using the 4-Digit Code. As a demonstration for how to interpret this figure; 388 patients received a 4-Digit Code Diagnosis of SE/AE (severe CNS abnormalities with confirmed PAE). Of the 388 patients, 178 received a "FASD without the Face" diagnosis, 49 received an "At-Risk" classification and 161 received a "Not FASD" classification using the Canadian diagnostic system. All 49 At-Risk are <6 years with confirmed PAE. Over half have severe dysfunction, but do not meet the high PAE criteria for FASD. The remaining has microcephaly, but do not meet the severe dysfunction criteria for FASD. The 161 classified "Not FASD" have the same profile as those classified "At Risk", but all are > 6 years of age, thus will not present with both high PAE and severe dysfunction later in childhood as required for a Canadian FASD diagnosis.
Abbreviations: 4-Digit Code Categories A-V are case-defined in the Diagnostic Guide for FASD [5]. AE: alcohol exposed; A: alcohol exposure unknown; ND: Neurodevelopmental Disorder; Not FASD/A: Individuals who present with or without growth, facial, and/or CNS abnormalities, but are not under the umbrella of FASD because their prenatal alcohol exposure is unknown and they do not meet the criteria for FAS/A?. SE: static encephalopathy; SPF: Sentinel Physical Findings, individuals who present with growth deficiency and/or 1 to 3 FAS facial features, but have normal CNS structure and function; Normal: no evidence of growth, facial, or CNS structural/functional abnormalities. Age yrs; mean age in years at diagnosis.

Rank 4 FAS facial phenotype, introduced by the 4-Digit Code and adopted by the Canadian and Australian systems, has a specificity of >95% [17,20]. The FAS facial phenotype as defined by the Hoyme system is substantially relaxed relative to the 4-Digit Code Rank 4 facial phenotype (Figure 3) and has a substantially reduced specificity (71% to 75%) [19,32]. If the FAS facial phenotype is specific to PAE, validation studies should confirm the FAS facial phenotype is more prevalent among those with higher exposure and does not occur in individuals with confirmed absence of PAE.

One would also expect that the majority of (if not all) individuals presenting with the FAS facial phenotype would meet criteria for a diagnosis under the umbrella of FASD.

No association was observed between the prevalence of the Hoyme FAS facial phenotype and level of alcohol exposure. The Hoyme FAS facial phenotype was equally prevalent and highly prevalent in the Rank 3 (moderate exposure) and Rank 4 (high exposure) groups when alcohol exposure was classified in accordance with the 4-Digit Code (4-Digit Code Alcohol: Chi^2 0.95, p=0.33) (Figure

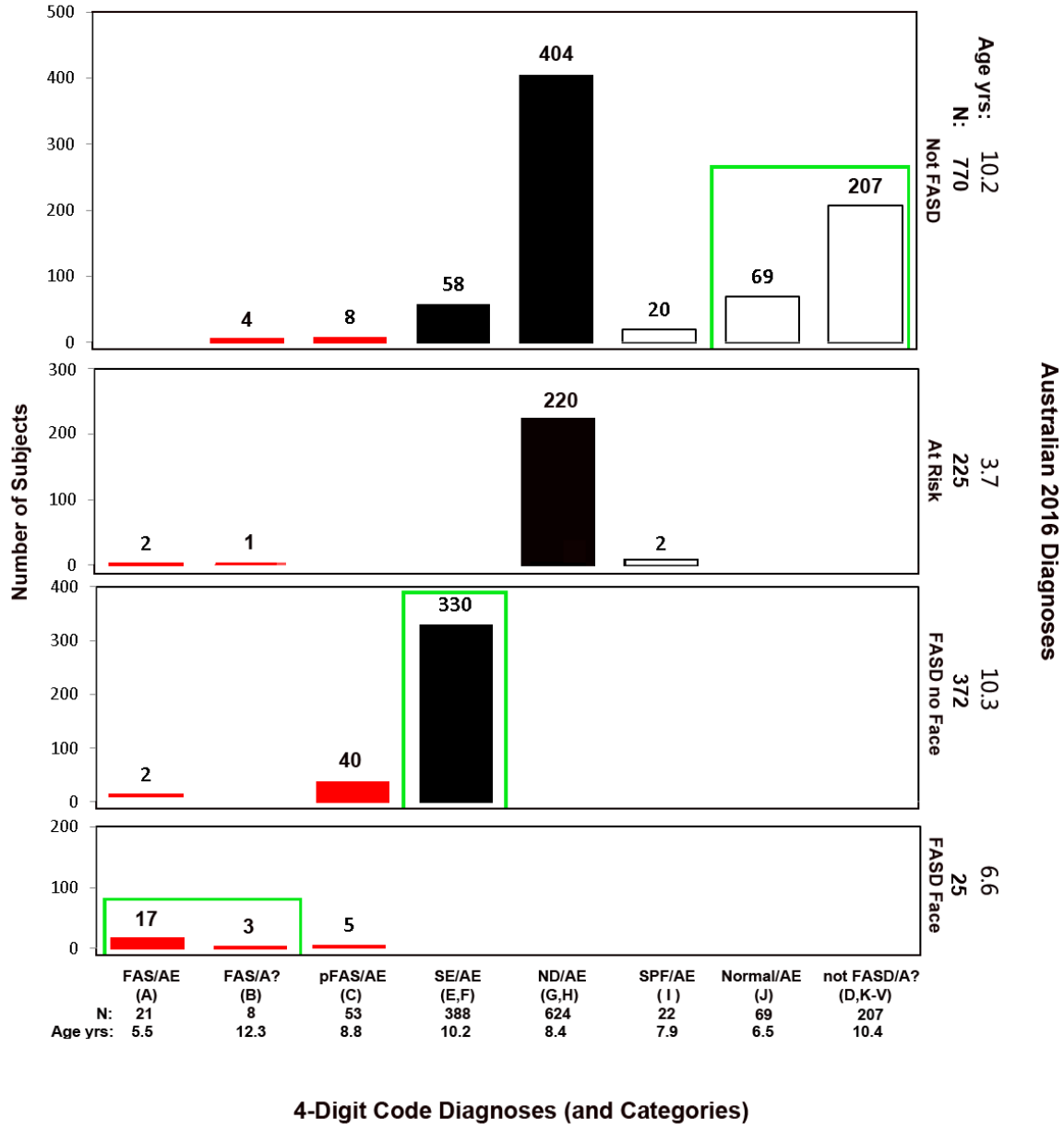


Figure 9. Cross-tabulation of the 4-Digit Code and Australian 2016 FASD Diagnostic Outcomes.
Diagnostic concordance (green boxes) between the 4-Digit Code and Australian 2016 systems was observed in 45% (626/1,392) of the patients. Red bars reflect FAS and PFAS diagnoses using the 4-Digit Code. Black bars reflect the rest of the FASD spectrum using the 4-Digit Code. As a demonstration for how to interpret this figure; 624 patients received a 4-Digit Code Diagnosis of ND/AE. Of the 624 patients, 220 received an "At Risk" classification, and 404 received a "Not FASD" classification using the Australian diagnostic system. The 404 patients classified "not FASD" by the Australian system were all > 6 years of age with confirmed PAE (half with confirmed high PAE). 87% had 1 or 2 (but not 3) domains of severe dysfunction and all had multiple domains of moderate dysfunction. The Australian system does not classify patients with this level dysfunction under the umbrella of FASD. Primate research documents moderate dysfunction is the most prevalent outcome caused by prenatal alcohol exposure (Figure 6). The 220 patients classified as "At Risk" by the Australian system have the same exposure and moderate dysfunction profile, but are all<6 years of age. These 220 are identified as "At Risk" because they are at risk of presenting with severe dysfunction later in childhood, and thus still at risk for FASD.
Abbreviations: 4-Digit Code Categories A-V are case-defined in the Diagnostic Guide for FASD [5]. AE: alcohol exposed; A?: alcohol exposure unknown; ND: neurodevelopmental disorder; Not FASD/A?: Individuals who present with or without growth, facial, and/or CNS abnormalities, but are not under the umbrella of FASD because their prenatal alcohol exposure is unknown and they do not meet the criteria for FAS/A?. SE: static encephalopathy; SPF: Sentinel Physical Findings, individuals who present with growth deficiency and/or 1 to 3 FAS facial features, but have normal CNS structure and function; Normal: no evidence of growth, facial, or CNS structural/functional abnormalities. Age yrs; mean age in years at diagnosis.

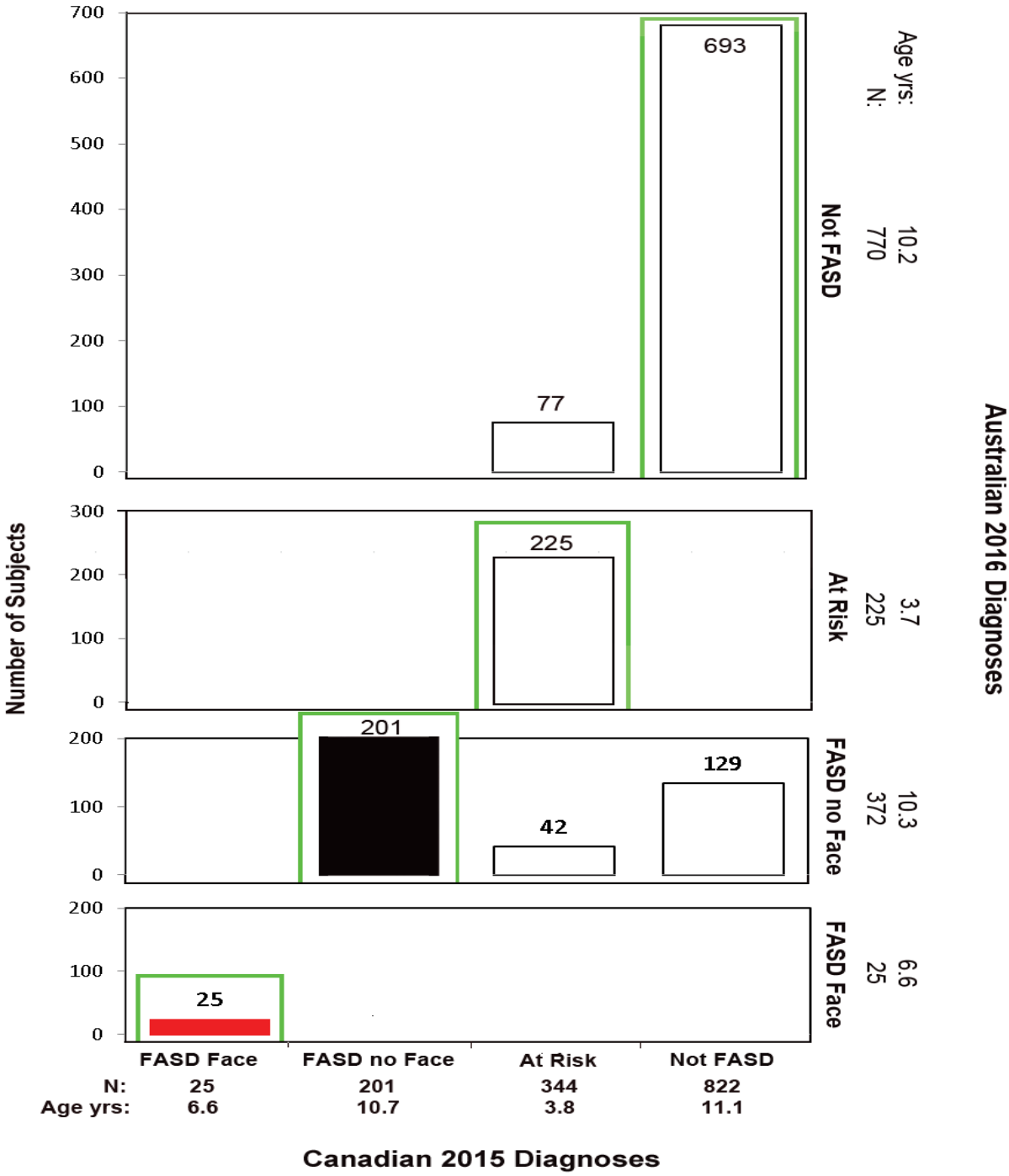


Figure 10. Cross-tabulation of the Canadian 2015 and Australian 2016 FASD Diagnostic Outcomes.
Diagnostic concordance (green boxes) between the Canadian 2015 and Australian 2016 systems was observed in 82% (1,144/1,392) of the patients with the majority of the concordance due to 693 of the patients receiving a "Not FASD" diagnosis by both systems. This higher level of concordance is due to the fact that the Australian system adopted most of the criteria used by the Canadian system, with one important exception. The Canadian system requires confirmed high PAE. The Australian system requires confirmed PAE at any level. Red bars reflect "FASD with and without the Face" diagnoses using the Canadian system. As a demonstration for how to interpret this figure; 822 patients received a Canadian classification of "Not FASD". Of the 822 patients, 129 received an "FASD without the Face" and 693 received a "Not FASD" classification using the Australian diagnostic system. The 129 diagnosed "FASD with no Face" by the Australian system all had confirmed PAE, but the level did not meet the Canadian requirement for high exposure. Red bars reflect "FAS with the Face" diagnoses using the Canadian system. Black bars reflect "FASD without the Face" diagnoses using the Canadian system. Abbreviations: Age yrs; mean age in years at diagnosis.

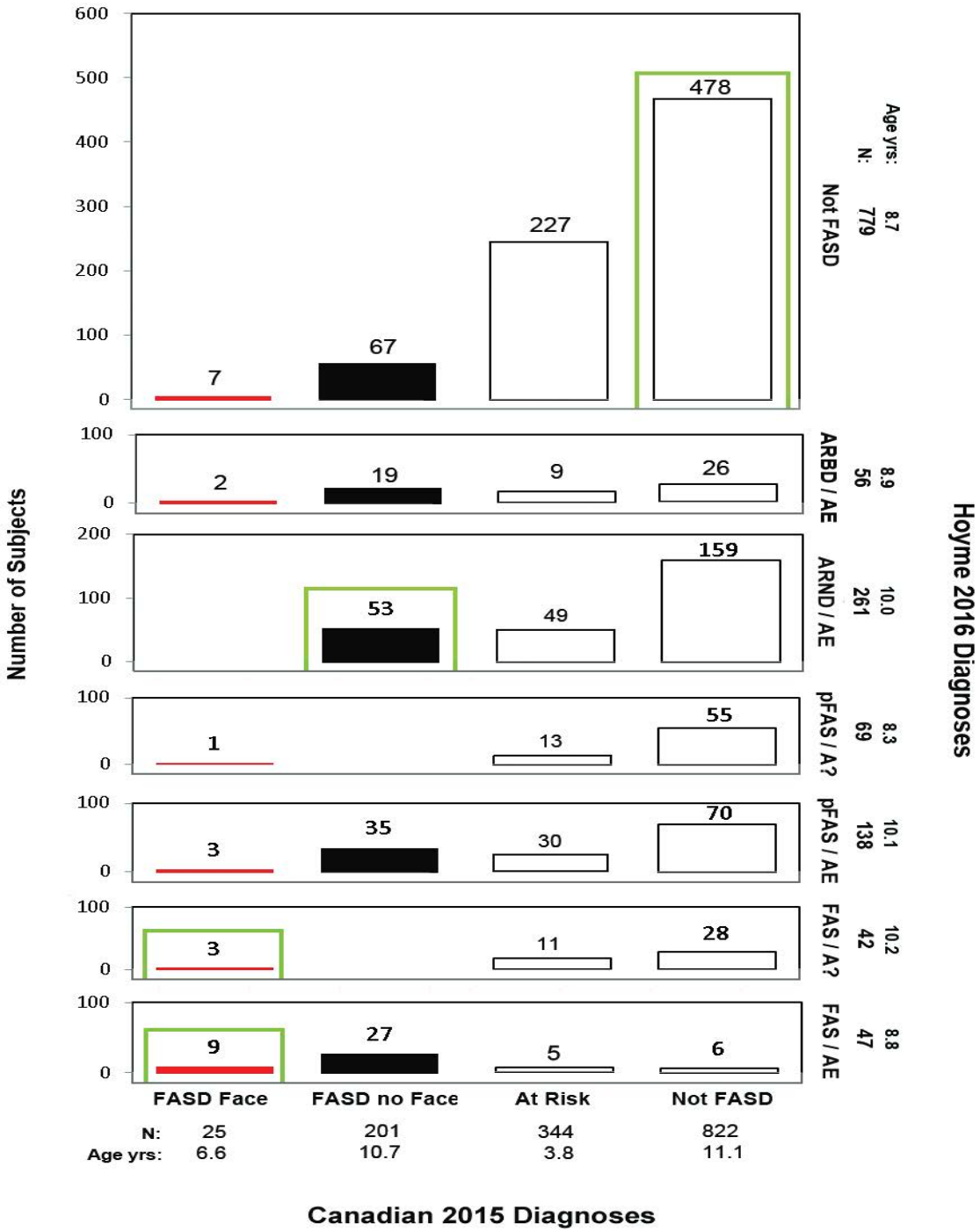


Figure 11. Cross-tabulation of the Canadian 2015 and Hoyme 2016 FASD Diagnostic Outcomes.
Diagnostic concordance (green boxes) between the Canadian 2015 and Hoyme 2016 systems was observed in 41% (569/1,392) of the patients with the majority of the concordance due to 740 of the patients receiving a "Not FASD" diagnosis by both systems. Red bars reflect "FAS with the Face" diagnoses using the Canadian system. Black bars reflect "FASD without the Face" diagnoses using the Canadian system. As a demonstration for how to interpret this figure; 822 patients received a Canadian classification of "Not FASD". Of the 822 patients, 28 received a diagnosis of "FAS/A?, 70 received a diagnosis of pFAS/AE, 55 received a diagnosis of pFAS/A?, 159 received a diagnosis of ARND/AE and 504 received a classification of "Not FASD" using the Hoyme system. Most of the 159 with FAS/PFAS presented with the relaxed Hoyme FAS facial phenotype. Only 8 of the 159 presented with the Canadian FAS face (4-Digit Code Rank 4). The remaining 151 patients with the Hoyme FAS face presented with the following 4-Digit Face Ranks: Rank 1 normal face 15%, Rank 2 mild face 59%, and Rank 3 moderate face 21%. These relaxed FAS facial phenotypes were used by the Hoyme system to overcome the unknown PAE among the 70 patients diagnosed pFAS/A? and the 28 patients diagnosed FAS/A? Abbreviations: Age yrs; mean age in years at diagnosis.

12A). The Hoyme FAS facial phenotype was also equally prevalent and highly prevalent when alcohol exposure was classified in accordance with the Hoyme system (Chi^2 0.01; p=0.92) (Figure 12B). In contrast, the 4-Digit Code Rank 4 FAS face was 5 times more prevalent in the Rank 4 high exposure group than the Rank 3 moderate exposure group (Chi^2 17.5; p=0.000) (Figure 12C). The association between the 4-Digit FAS face and alcohol was weakened substantially when the Hoyme criteria for alcohol exposure were used (Chi^2 6.1, p=0.02). The 4-Digit FAS face was only 2-fold more prevalent in the Hoyme exposed group relative to the Hoyme unknown/too-low exposure group (Figure 12D).

Of the 552 patients with the Hoyme FAS face, 43% did not receive a diagnosis under the umbrella of FASD using the Hoyme system. In contrast, all 54 individuals with the 4-Digit Code Rank 4 FAS face met criteria for a diagnosis under the umbrella of FASD using the 4-Digit Code.

When the Hoyme and 4-Digit Code FAS facial criteria were applied to an adolescent with high function (FSIQ 123) and confirmed absence of PAE (4-Digit Code 1211), she met the Hoyme criteria for the full FAS facial phenotype (Figure 3C). In contrast, her facial phenotype was classified within the normal range by the 4-Digit Code (Face ABC-Score BBC, Face Rank 2).

Should moderate dysfunction be included under the umbrella of FASD? Does PAE cause moderate dysfunction?

All four diagnostic systems include a diagnosis under the umbrella of FASD for individuals that present with severe dysfunction (3 or more domains of function, 2 or more SDs below the mean). Only the 4-Digit Code and Hoyme systems, however, include diagnostic classifications (ND/AE and ARND respectively) for individuals who present with moderate dysfunction (1 or 2 domains of function 2 or more SDs below the mean). Should moderate dysfunction be included under the umbrella of FASD? Does PAE cause moderate dysfunction? To address this question, the 4-Digit Code was applied to our nonhuman-primate model of FASD [4] to document the distribution of diagnostic (FAS/PFAS, SE/AE, ND/AE and Not FASD/AE) outcomes when the only risk factor present was PAE. The primates had been exposed weekly to binge exposures equivalent to a six-pack of beer for the first 3, 6 or entire 24 weeks of gestation (mean maternal peak plasma ethanol concentrations ranged from 176 to 271 mg/dl). The primate model confirmed PAE causes a spectrum of outcome (FAS/PFAS 5%, SE/AE 31%, ND/AE 59%, and Not FASD/AE 5%) with moderate dysfunction (ND/AE) being the most prevalent outcome (Figure 6A). The 4-Digit Code was the only system that produced a near identical distribution of diagnoses across the full spectrum (including 53% ND/AE) illustrated in Figure 6B. The Australian and Canadian outcomes were in greatest contrast with the primate model due to their exclusion of moderate dysfunction from the spectrum. The Australian system produced a good match to the primate model for the severe end of the spectrum (FASD with and without the Face), whereas the Canadian system's requirement for confirmed high PAE results in a poor match between their diagnostic outcomes and the primate model. The Hoyme criteria produce outcomes across the full spectrum, but the distribution did not match the primate model. The relaxed facial criteria placed far more in the FAS/PFAS category and far less in the moderate and severe dysfunction categories. The Australian, Canadian and Hoyme systems placed 51% to 81% of patients with PAE in the "Not FASD" category, in contrast to the 5% observed in the primate model.

Does the pattern and magnitude of dysfunction among patients with moderate dysfunction warrant and qualify them for intervention services?

Of the 402 patients with ND/AE who were 6 years of age or older at the time of their diagnosis, 83% presented with 1-2 domains of severe dysfunction (2 or more SDs below the mean) and 1-6 domains of moderate dysfunction (1 to 1.9 SDs below the mean) (Figure 13). The patterns of moderate dysfunction (1 to 1.9 SDs below the mean) across 9 domains of function (intellect, adaptation, achievement, memory-executive function, language, motor, mental health, behavior and development) is comparable between patients diagnosed with ND/AE, SE/AE and FAS/PFAS using the 4-Digit Code (Figure 14A). The patterns of severe dysfunction (2 or more SDs below the mean) across 9 domains of function is less prevalent among patients with ND/AE than SE/AE and FAS/PFAS (by definition), but present nonetheless (Figure 14B). The magnitude and breadth of dysfunction observed among patients with ND/AE warrant identification and intervention.

The outcomes associated with FASD present along clinically meaningful continuums. Collapsing these continuums to dichotomous (present, absent) scales can hinder clinical practice and research efforts

The following serves as just one of many examples of how collapsing a continuous outcome into a dichotomous (present, absent) scale can adversely impact clinical practice (e.g., the ability to render an accurate diagnosis and predict those at greatest risk) and research efforts (e.g., the power to detect causal associations). The FAS facial phenotype serves two clinically vital functions in the field of FASD. 1) The Rank 4 FAS facial phenotype is so highly specific to PAE it can be used to confirm PAE when a history of PAE is not available for a patient [20,17]. 2) The phenotype presents along a clinically informative continuum that is highly correlated with (and predictive of) the magnitude of CNS damage in a young patient [9,17]. Linear correlations serve as one of the most powerful metrics for identifying causal associations. Identification of causal and predictive associations serves to validate and inform clinical practice. For example, the causal link between the Rank 4 face and alcohol allows the clinician to render a diagnosis of FAS when PAE is unknown. The ability of the Rank 3 face to predict severe CNS dysfunction later in childhood allows the clinician to identify and provide early intervention to infants/toddlers at high risk. When the continuum of expression of the FAS facial phenotype is collapsed into a dichotomous (present, absent) scale, the clinical utility of the phenotype is diminished or even invalidated. For example, as illustrated in Figure 15, a significant linear correlation between the magnitude of expression of the FAS facial phenotype and the prevalence of severe CNS dysfunction (CNS Rank 3) is identified when the facial phenotype is recorded on the 4-point ordinal scale used by the 4-Digit Code (Chi^2 linear trend=10.5, p=0.001) (Figure 15). It is clear from the pattern of association depicted by the blue line (Figure 15) that the prevalence of CNS dysfunction associated with the Rank 1 and 2 facial phenotypes (32% and 36%) are distinctly lower than the prevalence of dysfunction associated with the Rank 3 and 4 facial phenotypes

(50% and 50%). The 4-point scale preserves the clinician's ability to use the Rank 3 and Rank 4 faces to predict which toddlers are at highest risk of severe CNS dysfunction [9]. The 4-point scale also preserves the clinician's ability to use the Rank 4 FAS facial phenotype to serve as confirmation of PAE when a history of PAE is not available. Both these functions are vital in a clinical setting. When the magnitude of expression of the FAS facial phenotype is collapsed into just two categories (present, absent), as introduced by the Hoyme, Canadian and Australian systems, one or both of these clinical functions are lost. For example, the Canadian and Australian systems collapsed the FAS face into (Present: Rank 4; Absent: Ranks 1, 2 and 3). In so doing, the systems preserved the high specificity of the Rank 4 face and thus the important clinical ability to use the Rank 4 face as confirmation of PAE when a history of PAE is unavailable. But, by collapsing the Rank 3 face with the Rank 1 and 2 faces, the Australian and Canadian systems lost the clinical ability to predict which infants/toddlers (those with the Rank 3 face) will present with severe brain dysfunction later in childhood [9]. The significant linear correlation between the FAS facial phenotype and prevalence of severe dysfunction detected by the 4-Digit Code ordinal scale (blue line in Figure 15) was rendered insignificant by the Australian/Canadian dichotomous facial scale (red line in Figure 14, Chi^2=0.5, p=0.46). The Hoyme system also collapsed the FAS face into a dichotomous (present, absent) scale, but used a different cut-point along the 4-Digit Code 4-point Face Rank scale (Present: Ranks 2,3, 4 and half of Rank 1; Absent: the other half of Rank 1) (Figure 3B). By combining Face Ranks 2, 3 and half of Rank 1 with Face Rank 4, the Hoyme system lost the high specificity of the Rank 4 FAS face and thus lost the clinical ability to use the "FAS face" as confirmation of PAE when a history of PAE is unavailable in a patient.

The Hoyme system also lost the clinical ability to predict which infants/toddlers will present with severe brain dysfunction later in childhood because the predictive ability of the Rank 3 and 4 faces are weakened by combining them with the normal Rank 1 and 2 facial phenotypes. The significant linear correlation between the FAS facial phenotype and prevalence of severe dysfunction detected by the 4-Digit Code ordinal scale (blue line in Figure 15) was rendered insignificant (Chi^2=4.7, p=0.10) by the Hoyme dichotomous facial scale (black line in Figure 15).

Discussion

Contrasts in diagnostic outcomes

The four systems produced markedly different outcomes. Eighty-two percent of patients were diagnosed with FASD by at least one of the four systems, but only 11% of patients were diagnosed with FASD by all four systems. Eight percent of patients were diagnosed with FAS by at least one of the 4 systems, but only 1% was diagnosed with FAS by all four systems. The proportion of patients diagnosed with FAS, severe dysfunction, moderate dysfunction, and FASD overall varied significantly across the systems (4-Digit: 2%, 28%, 45%, ≤79%; Hoyme: 6%, 5%, 14% 44%; Australian: 2%, 26%, 0%, 29%; and Canadian: 2%, 14%, 0%, 16%) (Table 4).

Five factors accounted for the greatest contrasts in diagnostic outcomes between the four systems.

1. Extensive evidence supports the inclusion of individuals with moderate dysfunction (ND/AE) under the umbrella of FASD. The pattern and magnitude of dysfunction among patients with moderate dysfunction warrant and qualify them for intervention services. Exclusion of moderate dysfunction by the Canadian and Australian systems prevented 53% of patients with confirmed PAE from receiving a FASD diagnosis with the greatest impact on children less than 6 years of age. Individuals with PAE present with the full spectrum of CNS dysfunction from moderate to severe in Table 3 [1,33,34]. The evidence that supports inclusion of moderate dysfunction (ND/AE or moderate ARND) under the umbrella of FASD is as follows. First, and most importantly, hundreds of laboratory-based studies, including our nonhuman-primate studies in Figure 6A [4,35], confirm prenatal alcohol exposure causes moderate dysfunction. Not only does it cause moderate dysfunction, but moderate dysfunction is the most common outcome. In this study population of 1,177 with PAE and the larger population from which it was drawn (2,550 alcohol-exposed patients evaluated at the WA FASDPN clinics over the past 20 years), 45-53% met the criteria for ND/AE [17]. ND/AE was the most common outcome, exceeding the prevalence of FAS/PFAS (6-10%) and SE/AE (24-33%) combined. It is important to note that alcohol is not the only risk factor contributing to adverse outcomes in the FASDPN patient population (see Figure 21 in Astley [17]). So what would the diagnostic distribution look like if alcohol was the only risk factor? To answer that question, we applied the 4-Digit Code to the outcomes observed in our primate model of FASD [4] (Figure 6A). Remarkably, the distribution of FAS/PFAS (5%), SD/AE (31%) and ND/AE (59%) was near identical to that observed in our FASD clinical population, with ND/AE being the most common outcome. And just like in our primate model, individuals with ND/AE have alcohol exposures as high as those with FAS/PFAS and SE/AE (see Figure 22 in Astley [17]). Are these moderate impairments in brain function associated with underlying CNS structural abnormalities? Again, the answer is yes. Our MRI study confirmed at least 43% of individuals with ND/AE have significant CNS structural abnormalities [36] (see also Figure 15C in Astley [17]). Our extensive experience in the WA FASDPN confirms that it is the children with moderate dysfunction that fair the worst and are often in most need of diagnostic identification and intervention. These are the children that too often slip through the cracks. Their disabilities are often not severe enough in the cognitive domain to qualify them for services (only 3% have an IQ less than 70) [17], but severe enough across many other domains (Figures 13 and 14) (see also Figure 23 in Astley [17]) to adversely impact their ability to fully engage in school and live productive, independent lives. Children with ND/AE received as many intervention recommendations as children with FAS/PFAS and SE/AE in our patient population (see Figure 24 in Astley [17] and Table 4 in Jirikowic et al [37]). And perhaps most importantly, the diagnosis of ND/AE provided caregivers with as much access to services as caregivers of children with FAS/PFAS and SE/AE. Caregivers also reported the interventions worked as well for their children with ND/AE as did caregivers of children with FAS/PFAS and SE/AE (see Figure 31 in Astley [17]).

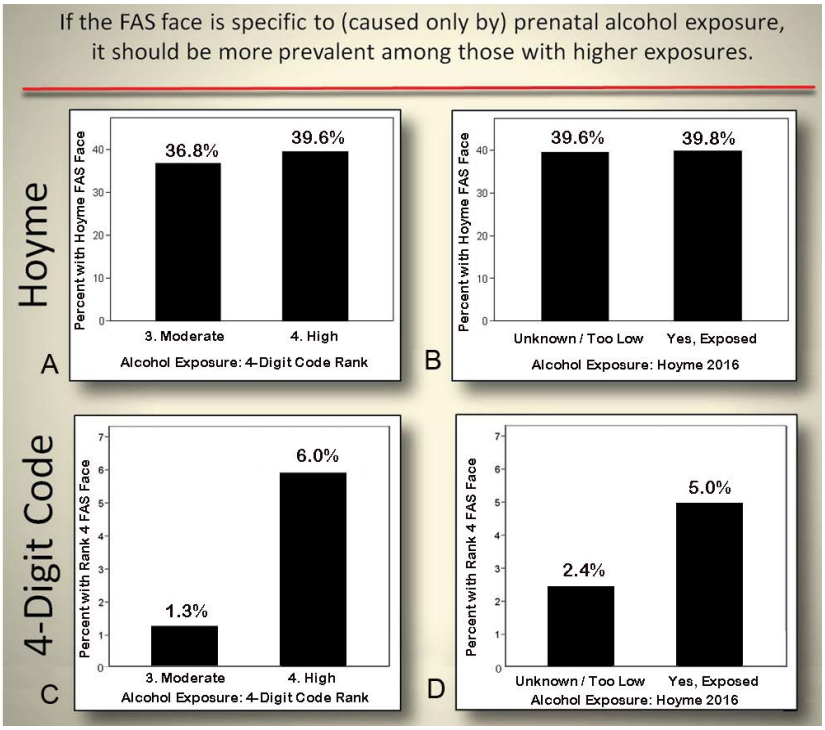


Figure 12. Only the 4-Digit Code FAS Face was Significantly More Prevalent Among Patients with Higher Alcohol Exposure.
The Hoyme 2016 [10] FAS face was equally prevalent and highly prevalent in the moderate (4-Digit Code Alcohol Rank 3) and high (4-Digit Code Alcohol Rank 4) alcohol exposure groups (Chi^2 0.9, p=0.33). B) The Hoyme FAS face was also equally prevalent and highly prevalent between those that did and did not meet the Hoyme alcohol exposure criteria (Chi^2 0.01, p=0.92). In contrast, the 4-Digit Code FAS facial phenotype was highly correlated with measures of prenatal alcohol exposure. C) The 4- Digit Code Rank 4 FAS face was 5 times more prevalent in the high exposure group (4-Digit Code Alcohol Rank 4) than the moderate exposure (Digit Code Alcohol Rank 3) group Chi^2 17.5, p=.000). D) The association between the 4-Digit Code Rank 4 FAS facial phenotype and alcohol was substantially weakened when the Hoyme 2016 criteria for alcohol exposure were applied (Chi^2 6.1, p=0.02). The 4-Digit FAS face was only 2-fold more prevalent in the Hoyme et al. exposed group relative to the Hoyme et al. unknown/too low exposure group.

It is important to clarify that, when we report above that there is extensive evidence to support inclusion of ND/AE under the umbrella of FASD, we are not stating that all individuals who meet the criteria for ND/AE have FASD. By definition all individuals with Fetal Alcohol Spectrum Disorder have a disorder caused, at least in part, by their prenatal alcohol exposure. But not all individuals with ND/AE necessarily have a FASD. Only the subset of individuals whose neurobehavioral disorder was caused, at least in part, by their prenatal alcohol exposure, have a FASD. This is a current inherent weakness in the umbrella term FASD. In the absence of a biomarker that can causally link an individual's alcohol exposure with their neurodevelopmental disorder, there is no way to identify which individuals with ND/AE have FASD. This same argument applies to the diagnostic classifications of SE/AE, ARND and "FASD without the Face". Not all individuals who meet the criteria for SE/AE, ARND and "FASD without the Face" necessarily have FASD. Only the subset of individuals whose CNS abnormalities were caused, at least in part, by their prenatal alcohol exposure has FASD. And once again the field of FASD currently has no way (no biomarker) to identify this subset. Until such a biomarker is identified, if such a biomarker exists, the 4-Digit Code elects to label these categories with terms that do not imply causality.

2. The more stringent Hoyme and Canadian alcohol exposure criteria prevented 47%-59% of patients with confirmed PAE from receiving a diagnosis of FASD. In a clinical setting, one is not in a position to know how accurate the exposure was recalled and reported. Setting a threshold implies the details of all reported exposures are accurate and no fetus can be harmed by exposures below the threshold. Neither of these statements is true and the latter sends a confusing public health message that lower levels are safe. Recognizing this, the 4-Digit Code requires a confirmed exposure, but does not set a threshold. It is interesting to note that Petryk et al., [38] reported similar findings when they retrospectively assessed the impact of applying the 2016 Canadian guidelines to 119 patients with confirmed PAE (4-Digit Code Alcohol Ranks 3 or 4) and severe structural and/or functional CNS abnormalities (4-Digit Code CNS Ranks 3 and/or 4). In the Petryk study, the more stringent Canadian exposure criteria would have prevented 71% of the individuals from receiving a diagnosis under the umbrella of FASD because the reported exposure would not have met the required threshold.
3. Individuals with FASD are born with FASD, but the Hoyme, Canadian and Australian guidelines prevent most children under 3 or 6 years of age with confirmed PAE and structural or functional CNS abnormalities from receiving a diagnosis under the umbrella of FASD.

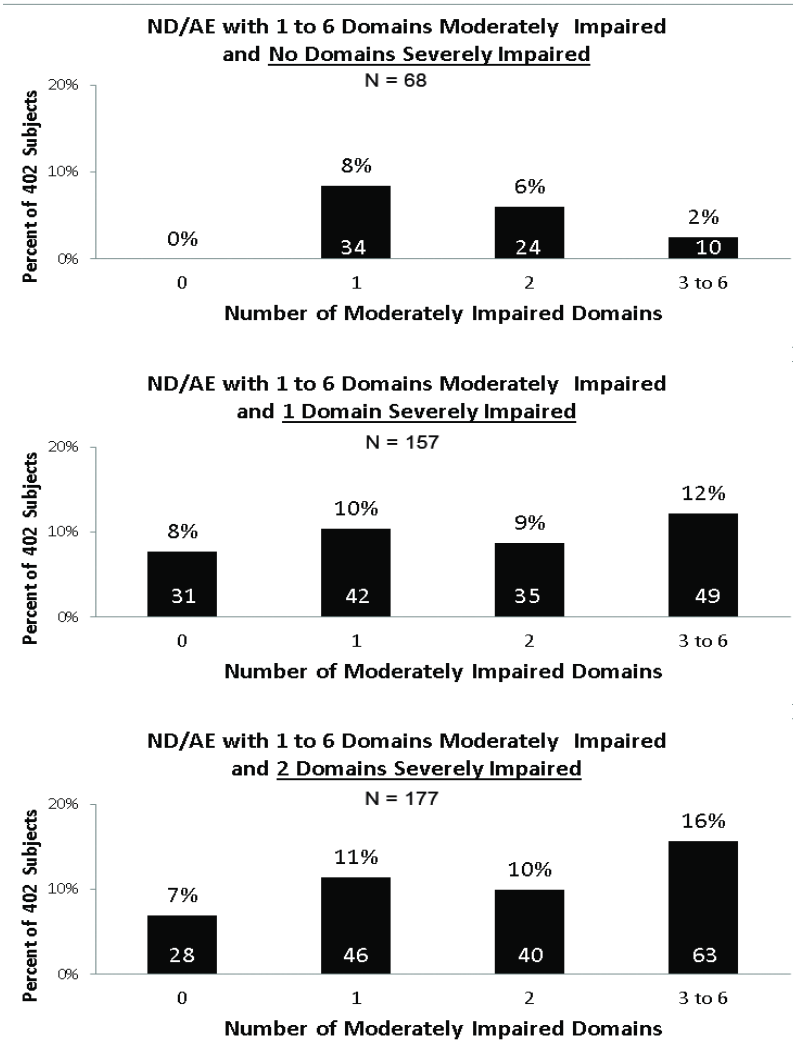
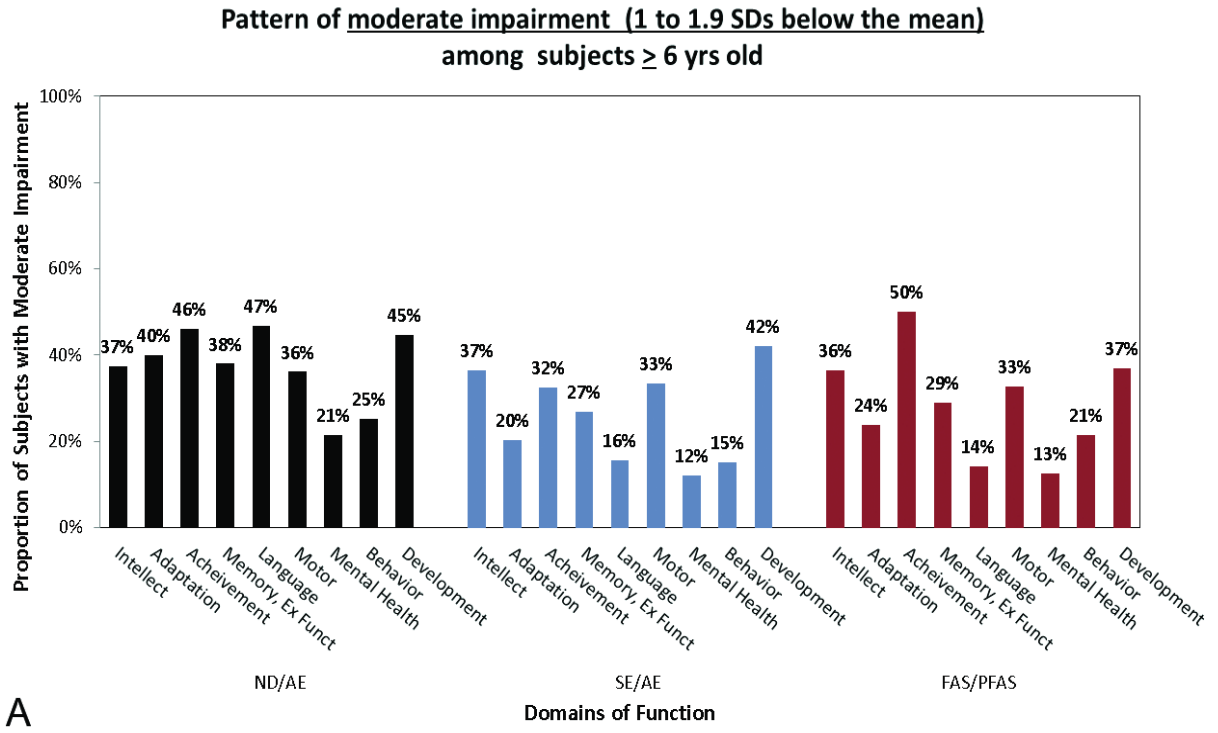


Figure 13. Distribution of Moderate and Severe CNS Dysfunction Among Patients Diagnosed with ND/AE by the 4-Digit Code.
Of the 402 patients diagnosed with ND/AE by the 4-Digit Code who were 6 years of age or older at the time of their diagnosis, 83% (334/402) presented with 1-2 domains of severe dysfunction (2 or more SDs below the mean) and 1-6 domains of moderate dysfunction (1 to 1.9 SDs below the mean). Domains of function included: intellect, adaptation, achievement, memory-executive function, language, motor, mental health, behavior and development, as illustrated in Figure 14. As a demonstration for how to interpret this figure; the bar on the bottom right documents 63 of the 402 patients (16%) presented with 2 domains of severe dysfunction and 3 to 6 additional domains with moderate dysfunction.

The 4-Digit Code allows a diagnosis of FAS/PFAS at birth based solely on physical abnormalities (growth deficiency, FAS face and microcephaly), having confirmed empirically that over 90% of alcohol-exposed infants and toddlers who present with one or more of the sentinel physical features of FAS as defined by the 4-Digit Code (microcephaly ≤3rd percentile, a Rank 4 FAS facial phenotype, or Rank 4 growth deficiency) will present with severe CNS Rank 3 dysfunction later in childhood [9]. In contrast, the Hoyme system requires both reduced head circumference and CNS dysfunction for an FAS/PFAS diagnosis, preventing a diagnosis in infant/toddlers too young to be assessed for CNS dysfunction. In addition, the Hoyme system does not permit a diagnosis of ARND in a child<3 years of age. The Canadian and Australian systems require severe CNS dysfunction for an FASD diagnosis, preventing all children with PAE who present with microcephaly and/or moderate CNS dysfunction from receiving a diagnosis of FASD, with one exception. If the child with PAE presents with microcephaly and the FAS facial phenotype, a diagnosis of "FASD with the Face" can be made in the absence of CNS dysfunction, based on the finding of the 4-Digit Code that microcephaly and the Rank 4 FAS facial phenotype are highly predictive of severe CNS dysfunction later in childhood. Growth deficiency was as strong a predictor of severe brain dysfunction in infants with PAE as the FAS facial phenotype and microcephaly, but the Canadian and Australian systems excluded growth deficiency from their FASD criteria. While this one exception (microcephaly and the FAS facial phenotype) allowed a diagnosis of "FASD with the Face" in a small number of children (n=6)<6 years



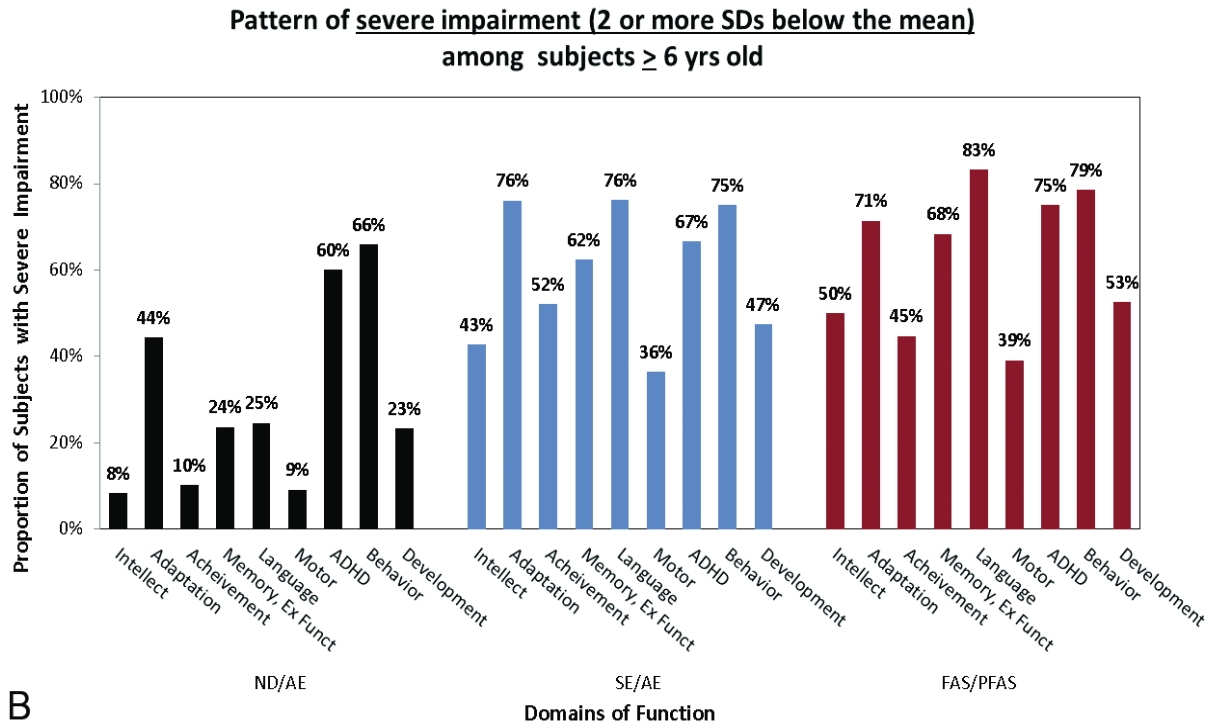


Figure 14. Patterns of Dysfunction Among Patients > 6-years-old with 4-Digit Code Diagnoses ND/AE, SE/AE or FAS/PFAS.
The proportion of patients presenting with moderate dysfunction (1 to 1.9 SDs below the mean) across 9 domains of function (intellect, adaptation, achievement, memory-executive function, language, motor, mental health, behavior and development) is comparable between patients diagnosed with ND/AE, SE/AE and FAS/PFAS using the 4-Digit Code. B) The proportion of patients presenting with severe dysfunction (2 or more SDs below the mean) across 9 domains of function is less prevalent among patients with ND/AE than SE/AE and FAS/PFAS (by definition), but present nonetheless.

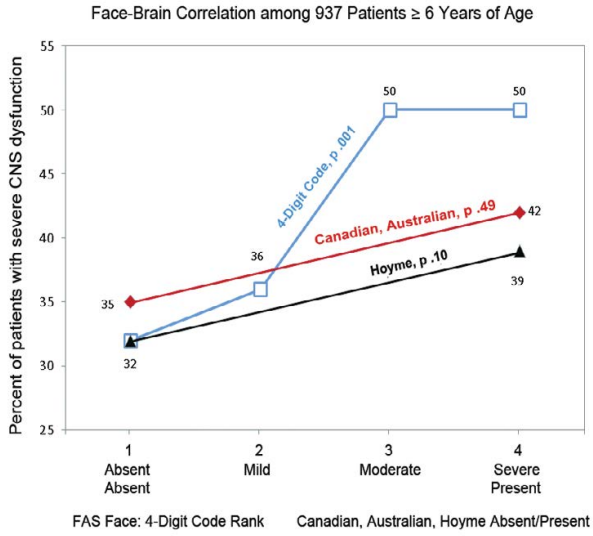


Figure 15. Significant Correlation Between Face and Brain Lost when the Facial Phenotype is Reduced to Present/Absent.

The FAS facial phenotype presents along a clinically meaningful continuum. A significant correlation between the magnitude of expression of the FAS facial phenotype and the prevalence of severe CNS dysfunction (CNS Rank 3) is identified when the facial phenotype is recorded on the 4-point ordinal scale used by the 4-Digit Code (blue line: Chi^2 linear trend=10.5, p=0.001). Linear trends serve as one of the most powerful metrics for identifying causal associations. When the magnitude of expression of the FAS facial phenotype is collapsed into just two categories (present, absent), as introduced by the Hoyme, Canadian and Australian systems, the significant correlation between face and brain is lost. Not only does a dichotomous scale have less statistical power to identify real associations, but where the ordinal scale is bisected impacts the validity of the dichotomous scale. It is clear from the pattern of association depicted by the blue line that the prevalence of CNS dysfunction associated with the Rank 1 and 2 faces (32% and 36%) are distinct from the prevalence of dysfunction associated with the Rank 3 and 4 faces (50% and 50%) The most clinically valid cut-point to bisect the ordinal scale would be between Ranks 2 and 3. The Canadian and Australian systems used a cut-point between Ranks 3 and 4 to dichotomize the FAS facial phenotype (Present=Rank 4; Absent=Ranks 1, 2 and 3). The Hoyme system used a cut-point halfway through Rank 1 to dichotomize the face (Present=Ranks 2, 3, 4 and half of Rank 1; Absent=the other half of Rank 1) (Figure 3B). Both dichotomous scales (red and black lines) failed to identify the significant correlation that exists between the severity of the FAS facial phenotype and prevalence of severe brain dysfunction (Canadian and Australian: Chi^2=0.5, p=0.46; Hoyme: Chi^2=4.7, p =0.10).

old, the majority of the 407 children with PAE under 6 years of age (n=238) failed to receive a diagnosis under the umbrella of FASD because they presented with moderate dysfunction (ND/AE); a diagnosis excluded from the Canadian and Australian systems. Failure to identify and diagnose FAS/D in children<6 years of age will prevent these high-risk children from receiving the benefits of early intervention.

4. Growth deficiency is significantly associated with PAE, is as prevalent as the FAS facial features and CNS abnormalities, and is a highly predictive of severe CNS dysfunction among infants/toddlers. The Canadian and Australian systems removed growth deficiency as a criterion for FASD, yet growth deficiency was as strong a predictor of severe brain dysfunction in infants with PAE as the FAS facial phenotype and microcephaly. Decades of laboratory and clinical-based studies unequivocally confirm that PAE causes GD [39-43]. While many factors can impact growth, an empirical study conducted by Astley et al., [9] confirmed that postnatal short stature is significantly correlated with PAE (while low birth weight is significantly correlated with prenatal tobacco exposure). The study found growth deficiency was as prevalent as the other core diagnostic features of FASD (FAS facial phenotype and CNS structural abnormalities). Most importantly, growth deficiency among children with PAE is highly predictive of who will present with severe CNS dysfunction. This is especially important in children<8 years of age. Astley et al. [9]) found that among children under 8 years of age with PAE who present with height and/or weight at or below the 10th percentile (Growth Rank 2, 3 or 4); 57% with Growth Rank 2; 67% with Growth Rank 3 and 100% with Growth Rank 4 presented with severe CNS dysfunction after 8 years of age when they were old enough to participate in more sophisticated neuropsychological assessments. Of the 844 children classified as Not FASD, 633 had confirmed PAE. Of the 633 with confirmed PAE, 192 were under 8 years of age and 64 presented with Growth Rank 2, 3 or 4. Roughly 70% of these 64 children with confirmed PAE will likely present with severe CNS dysfunction after the age of 8 years, but are not identified as "At Risk" by the Canadian system. Of the 983 children classified as Not FASD by the Australian system, 773 had confirmed PAE. Of the 773 with confirmed PAE, 435 were under 8 years of age and 126 presented with Growth Rank 2, 3 or 4. Roughly 70% of these 126 children with confirmed PAE will likely present with severe CNS dysfunction after the age of 8 years, but are not identified as "At Risk" by the Australian system.

5. The relaxation of the Hoyme FAS facial phenotype criteria greatly increased the prevalence of FAS and PFAS diagnoses and jeopardized the validity of these FAS and PFAS diagnoses.

   - The Hoyme system classified 10 times more individuals with the FAS facial phenotype (n=552) than the 4-Digit Code (n=54) [10].
   - The Hoyme system produced 14 times more FAS/PFAS diagnoses with unknown alcohol exposure (n=111) than the 4-Digit Code (n=6) [10]. This is particularly concerning because 68 (61%) of these patients had 4-Digit Code Rank 1 or Rank 2 facial phenotypes that are, by our definition, clinically "normal". The Rank 1 and 2 phenotypes have no specificity to PAE [33]. The only reason FASD diagnostic systems permit a diagnosis of FAS to be made when PAE is unknown is because the facial phenotype is so highly specific to (caused only by) PAE, the face serves to confirm the exposure. If the facial phenotype defined by the diagnostic system is not confirmed to be highly specific to alcohol, then: 1) the diagnosis cannot be validly labeled FAS, PFAS or FASD because a causal link cannot be confirmed between the patient's alcohol exposure and their adverse outcomes, and 2) the facial phenotype cannot be validly used to confirm PAE when the history of exposure is unknown.

The 4-Digit Code allows a diagnosis of FAS to be made when PAE is unknown because the 4-Digit Code Rank 4 FAS facial phenotype is confirmed to be >95% specific to PAE [17, 20]. The 4-Digit Code does not allow a diagnosis of PFAS to be made when alcohol exposure is unknown, because the facial criteria for PFAS is relaxed to a Face Rank 3 (2.5 of the 3 features must be present), resulting in a subtle reduction in specificity. To err on the conservative side, the 4-Digit Code requires a confirmed exposure for PFAS

- In our previous study the relaxed Hoyme FAS facial phenotype demonstrated no association with PAE [10]. In contrast, the 4-Digit Code FAS facial phenotype demonstrated a strong, significant, linear association with PAE
- 70% of the 296 Hoyme FAS/PFAS cases had "normal" 4-Digit Code Face Ranks 1 or 2.
- 43% of the 552 patients with the Hoyme FAS face did not receive a diagnosis under the umbrella of FASD using the Hoyme system. In contrast, all 54 individuals with the 4-Digit Code Rank 4 FAS face met criteria for a diagnosis under the umbrella of FASD using the 4-Digit Code.
- Hoyme et al. [7] reports the relaxation of their facial criteria was to improve sensitivity and greater inclusion of children in the complete continuum of FASD. But, as demonstrated in this study, one need not sacrifice specificity for sensitivity to achieve greater inclusion across the full continuum of FASD. By documenting the FAS facial phenotype across its full continuum of expression (4-Digit Code Face Ranks 1, 2, 3 and 4), the 4-Digit Code preserves: 1) the high specificity of the Rank 4 FAS facial phenotype, 2) the clinically vital function of the Rank 3 face to predict severe brain dysfunction, and 3) the increased sensitivity to capture the full spectrum of FASD by inclusion of the Rank 2 face.

Contrasts in diagnostic tools

In addition to the contrasts in diagnostic criteria, the methods and tools used to measure the facial features are also markedly different. The authors of the Hoyme system promote the use of direct examination of facial features over the use of facial photographic software. The 4-Digit Code advises measuring the facial features from 2D digital photos using the FAS Facial Photographic Analysis Software [12]. Empirical studies have confirmed the superior accuracy of the photo versus direct method of facial measurement [13,15]. Significant contrasts also exist between the 4-Digit Code Lip-Philtrum Guide 1 and the Hoyme North American Lip/Philtrum Guide. As illustrated in Figure 3, although the Hoyme North American Lip/Philtrum Guide looks similar in appearance to the 4 Digit Code Lip-Philtrum Guide 1, these are not interchangeable tools. The lips ranked 1 through 5 on the Hoyme Guide do not match the lips ranked 1 through 5 on the 4-Digit Code Guide. The lips on the 4-Digit Code Guide become progressively thinner as Rank increases from 1 to 5. The lips on the Hoyme guide do not become progressively thinner as Rank increases (e.g., the Hoyme Rank 4 lip is thicker than the Hoyme Rank 3 lip). The images used to depict lip thinness for each Rank do not match between the two guides. When the Hoyme lips are mapped onto the 4-Digit Guide based on the objective measure of thinness (circularity), the Hoyme Rank 1, 2, 3, 4, and 5 lips are equivalent to the 4-Digit Code Lip Ranks 2, 2, 3, 2, and rank unknown, respectively. Both systems define the thin upper lip of FAS as Rank 4 or thinner. But the Hoyme Rank 4 lip is substantially thicker than the 4-Digit Rank 4 lip (it is equivalent to the 4-Digit Rank 2 lip).

The introduction of the Hoyme North American Lip/Philtrum Guide serves to further relax the Hoyme FAS facial phenotype. Only 2 of the 3 cardinal features are required and 2 of the 3 features are relaxed relative to the 4-Digit Code. The PFL is relaxed from the 3rd percentile to the 10th percentile and lip thinness is relaxed from Rank 4 to Rank 2 on the 4-Digit Code Lip-Philtrum Guide 1. An individual presenting with PFLs at the 10th percentile, a Rank 1 deeply grooved philtrum, and a 4-Digit Code Rank 2 moderately thick upper lip would meet the Hoyme criteria for the full FAS facial phenotype. The presence of a single, very minor anomaly (PFL at the 10th percentile) does not constitute a dysmorphic facial phenotype. In fact, it would be difficult to justify classifying any of these three features as minor anomalies outside the normal range. Yet, this facial phenotype is used by the Hoyme system to confirm PAE when PAE is unknown. Of the 102 patients with unknown PAE and the Hoyme FAS facial phenotype, 70% had a 4-Digit Code Rank 1 or Rank 2 facial phenotype. By definition, 4-Digit Face Ranks 1 and 2 reflect normal phenotypes with no specificity to PAE. This was clearly illustrated in our FASD MRI study [33]. Sixteen high-functioning adolescents with confirmed absence of PAE were enrolled as controls in that study. Ten presented with Rank 1 facial phenotypes and 6 presented with Rank 2 facial phenotypes (one of which illustrated in Figure 3C). Based on our previously published findings [10], the Hoyme North American Lip/Philtrum Guide is not a valid tool for use with the 4-Digit Code.

The quintessential role of the FAS facial phenotype

Why are the criteria used to define the FAS facial phenotype so important to the medical validity of all diagnoses under the umbrella of FASD, not just the diagnosis of FAS (or FASD with the Face)? When one makes a diagnosis of FAS, one is stating explicitly that the individual has a syndrome caused by PAE [17]. One is also stating explicitly that the biological mother drank alcohol during pregnancy and, as a result, harmed her child. These are bold conclusions to draw and are not without medical, ethical, and even legal consequences. When the FAS face is not specific to FAS and PAE, the validity of the entire FASD diagnostic system collapses. Here is why:

- The terms FAS and "FASD with the Face" are rendered invalid. If the face is NOT specific to (caused only by) alcohol, one can no longer label the condition fetal alcohol syndrome or fetal alcohol spectrum disorder. One can no longer confirm alcohol is causally linked to any of the outcomes (growth, brain, or face) in an individual patient.
- The diagnosis "FAS/Alcohol Unknown" is also rendered invalid. The FAS face can no longer serve as the confirmation of alcohol exposure when the exposure history is unknown.
- The terms "ARND" and "FASD without the Face" remain problematic. Since the CNS structural and functional abnormalities that define ARND and "FASD without the Face" are not specific to (caused only by) prenatal

alcohol, one is in no position to declare an individual's Neurodevelopmental Disorder is "Alcohol-Related" (ARND) or their Spectrum Disorder is caused by Fetal Alcohol (FASD).

With terms like ARND and "FASD without the Face", one feels compelled to require a significant exposure to alcohol to increase the odds that the individual's impairments may be caused, at least in part, by their alcohol exposure. This is a dangerous road to go down.

- Setting a threshold of significant exposure for Alcohol-Related Neurodevelopmental Disorder (ARND) or FASD does not confirm the patient's alcohol exposure caused their disorder.
- Alcohol is never the only risk factor contributing to the disorder.
- One is sending a potentially harmful message that lower levels of alcohol exposure are safe. As we illustrated in our previous publication (Figure 9) [10], individuals with reported PAE below the Hoyme or Canadian thresholds do present with full FAS. Either this individual was particularly vulnerable to the teratogenic insult of alcohol, or the reported exposure was not accurate. In a clinical setting, one is never in a position to know how accurate the exposure is recalled and reported. Setting a threshold implies the details of all reported exposures are accurate and no fetus can be harmed by exposures below the threshold.
- And one is blaming a woman for harming her child, when they have limited ability to make/defend such a claim.

The 4-Digit Code introduced the terms ND/AE and SE/AE back in 1997 [23]. These terms state the verifiable facts; the individual presents with a disorder and the individual was exposed to alcohol in utero. The terminology does not explicitly state their disorder is related to their alcohol exposure. In fact, the 4-Digit Code formally Ranks all other prenatal and postnatal risks factors to make clear that alcohol is never the only risk factor contributing to an individual's neurobehavioral disorder or static encephalopathy. In 2013, the DSM5 [44] took a similar nosological approach when it introduced the new term "Neurodevelopmental disorder / prenatal alcohol exposure" (ND/PAE) as a condition for further study. "ND/PAE is characterized by a range of developmental disabilities following exposure to alcohol in utero." ND/PAE is an example of "Other Specified Neurodevelopmental Disorder (315.8 (F88)).

When is it a FASD?

Fetal Alcohol Spectrum Disorders are, by definition, adverse outcomes caused by PAE. In the absence of an outcome that is specific to (caused only by) PAE (like the Rank 4 FAS facial phenotype), one cannot confirm or rule-out the role PAE played in an individual's CNS dysfunction.

- **Do all individuals with SE/AE, ND/AE, and ARND or "FASD without the Face" have FASD?** Not necessarily. Only the subset of individuals whose CNS dysfunction was caused (in whole or in part) by their alcohol exposure has FASD.
- **Which subset is that?** We currently have no way of knowing. This is why the 4-Digit Code refers to SE/AE and ND/AE as 'broadly" under the umbrella of FASD. Those with SE and ND caused by their alcohol exposure have FASD. Those with SE and ND that was not caused by their alcohol exposure do not have FASD.
- **But if they are exposed to high alcohol levels, can't we just assume alcohol caused their disability?** No. Not everyone exposed to high levels of alcohol presents with adverse outcomes. Among 2,576 alcohol-exposed individuals evaluated in the UW FASDPN Clinic to date, 26 with high exposures presented with full FAS (4-Digit Codes 4444) while 41 with high exposures presented with normal growth, face, and brain development (4-Digit Codes 1114) [17]. We also see discordant outcomes among fraternal twins. Among 20 twin pairs with identical high exposures, 5 had normal CNS function while their twin had moderate to severe CNS dysfunction [18].

  When an individual presents with high alcohol exposure and severe CNS dysfunction, but no FAS facial phenotype,as depicted in the diagnosis SE/AE (4-Digit Code 2134):

  - o If their CNS dysfunction is caused (at least in part) by their alcohol exposure, then their SE/AE is an FASD.
  - o If their CNS dysfunction was caused by other risk factors, not their alcohol exposure, then their SE/AE is NOT an FASD.
  - o The only way we can currently link alcohol to an individual's CNS dysfunction is if they present with a highly specific Rank 4 FAS face (FAS 2434).
- **If we cannot confirm alcohol caused a patient's disabilities, does this impact our ability to provide the patient with appropriate intervention?** No. Intervention recommendations and a patient's access to services and supports are based on their disabilities, not on what caused their disabilities. Twenty years of patient surveys [45] confirmed patients with a diagnosis of ND/AE and SE/AE were as likely to access and benefit from interventions as patients with FAS/PFAS. We did not have to label their disorder FAS or PFAS to qualify them for intervention and support services in Washington State.
- **If we cannot confirm a causal link between PAE and adverse outcomes in an individual patient, does this impact our ability to prevent FASDs?** No. To prevent FASD one must prevent PAE. To confirm efforts to prevent PAE are working, one needs to document PAE in a patient's medical record (regardless of outcome) and track the prevalence of PAE by birth cohort annually [46]. If one is reducing the prevalence of PAE, one is reducing the prevalence of FASD.

The four diagnostic systems produce different outcomes, but which one, if any, is correct?

Validation studies are required to confirm the accuracy, reproducibility, and medical validity of a diagnostic system. Validity is the degree to which a tool (or diagnostic system) is measuring what it purports to measure [47]. When the 4-Digit Code was introduced in 1997 [23,25], it was published as an empirical study confirming its superior performance to the gestalt [48,49] approach it was designed to replace. Since then, two decades of more extensive

laboratory, clinical, and public health empirical studies have comprehensively affirmed the validity of the FASD 4-Digit Code [17]. A clinician's guide for how to fully assess the performance of FASD diagnostic systems was presented in 2013 [17] and replicated with revision below in Table 5. The guide proposes 12 questions clinicians should ask to assess the performance of FASD diagnostic systems. The 4-Digit Code's performance meets all 12 criteria.

CONCLUSION

The needs of individuals and families impacted by FASD are best met when FASD diagnostic systems provide accurate diagnoses: 1) across the lifespan; 2) across the full spectrum of outcome (FAS, SE and ND); 3) across the full continuum of alcohol exposure; and 4) utilize diagnostic nomenclature that accurately reflects the association between outcome and alcohol exposure. These conclusions are supported by the current, published evidence base. In summary:

1. FASD is characterized by a spectrum of outcomes, not just severe outcomes.
   a. As illustrated in a primate model of FASD (Figure 6), PAE causes a full spectrum of outcome with moderate dysfunction (ND/AE) being the most prevalent outcome (59%).

      i) The vast majority (83%) of individuals with ND/ AE have 1 or 2 domains of severe dysfunction and multiple domains of moderate dysfunction. All require and benefit from intervention.
2. FASD is caused by the full continuum of PAE, not just high exposure.
   a. There is no known safe level of alcohol use during pregnancy.
   b. Requiring high PAE implies reported levels of PAE are reliably accurate. They are not.
   c. When high PAE is required for diagnosis, over half of individuals with confirmed PAE and severe CNS abnormalities do not receive a diagnosis of FASD.
   d. Over half of Individuals with the most severe outcome (FAS) have reportedly low to moderate PAE.
   e. The teratogenic impact of PAE is not just dependent on the timing and level of exposure. Twin studies confirm fetal genetics influences fetal vulnerability to PAE.
3. FASD is present at birth and should be diagnosed as early as possible, not after 3 or 6 years of age.
   a. Requiring severe CNS dysfunction prevents a diagnosis of FASD in a child too young to be fully assessed for CNS dysfunction.
   b. Excluding moderate CNS dysfunction from the umbrella of FASD prevents the early identification and intervention of children with confirmed PAE and moderate dysfunction (ND/AE).
   c. Excluding growth deficiency prevents the early identification of children who are at especially high risk for severe CNS dysfunction later in childhood.
   d. Children under 6 years of age with confirmed PAE and moderate dysfunction are not "At Risk" for FASD. Their alcohol exposures and moderate dysfunction have already occurred and warrant a diagnosis that documents their disability and qualifies them for early intervention.
4. FASD is characterized by growth deficiency, FAS facial features, and CNS structural/neurological/and functional abnormalities. Each present along clinically meaningful continuums and each are significantly correlated with PAE.
5. Growth deficiency is a core component of FASD.
   a. Growth deficiency (≤10th percentile) is as prevalent or more prevalent among individuals with PAE (32%) than the FAS facial phenotype (4%) and severe CNS abnormalities (39%).

Table 5. As clinicians assess the performance of FASD diagnostic guidelines, clinicians should ask the following questions [17].

1. Have properly designed studies been published to confirm the case definition for the FAS facial phenotype is highly specific (>95%) to FAS and alcohol (e.g., observed only among individuals with prenatal alcohol exposure and FAS)?
2. Was data used to empirically derive the diagnostic guidelines? Was the data drawn from a large, representative, and population-base?
3. Has the performance of the guidelines been empirically assessed (validated)?
4. Individuals are born with FAS/D. Can the diagnostic system identify FAS/D at birth and across the lifespan?
5. Growth deficiency, the FAS facial phenotype, CNS abnormalities, and alcohol exposure all present along clinically meaningful continuums. The FAS facial phenotype is not just present or absent. The brain is not just normal or abnormal. Do the Guidelines recognize/incorporate these important continuums?
6. Do the guidelines produce clinically distinct subgroups across the full spectrum (FAS, PFAS, SE/AE, ND/AE)?
A. Do brain imaging studies identify statistically significant contrasts between the FASD subgroups?
B. Individuals with FAS have more severe CNS dysfunction than individuals with "ARND". Do the Guidelines generate FAS and "ARND" groups that demonstrate this important contrast?
C. Do individuals who meet the criteria for FAS actually have FAS?
7. Can the guidelines detect unique alcohol exposure patterns between the FASD subgroups?
8. Can the diagnostic system be effectively and efficiently taught to interdisciplinary teams?
9. Are the guidelines confirmed to be reproducible? If two clinics use the guidelines, do they render the same diagnoses?
10. Do families report high satisfaction/confidence with the diagnostic process and outcome?
11. Are the names of the diagnoses (FAS, PFAS, SE/AE, ND/AE, ARND, ARBD, FASD with the Face, FASD without the Face) medically valid? Do they imply causality between alcohol and outcome that cannot be confirmed in the individual patient?
12. Do diagnoses under the umbrella of FASD qualify patients for intervention services that lead to improved outcomes?

b. The 4-Digit Code method for ranking growth deficiency successfully differentiates growth deficiency (postnatal short stature) associated with PAE from growth deficiency (low birth weight) associated with other risk factors like tobacco [9].

c. Growth deficiency (≤10th percentile) in infants/toddlers with PAE is as predictive of severe CNS dysfunction later in childhood as the Rank 4 FAS facial phenotype and microcephaly.

6. The 4-Digit Code Rank 4 FAS facial phenotype is the only outcome confirmed to date that is highly specific to (caused only by) PAE. This high specificity is required:

   a. To render a diagnosis of FAS when PAE is unknown.

   b. To confirm PAE is causally associated with outcomes in an individual patient.

   c. To validly label the disorder FAS or FASD.

7. Diagnostic nomenclature (e.g., ARND, FASD without the Face) should not infer a causal association between a patient's PAE and adverse outcomes when there is no evidence to validate such an inference.

   a. Inferring causation may erringly impugn some birth mothers.

   b. Effective intervention and prevention does not require confirmation of causation.

ETHICAL APPROVAL

This study was approved by the University of Washington Human Subjects Division.

AUTHOR CONTRIBUTION

All authors are members of the interdisciplinary FASD diagnostic team and participated in the interpretation and reporting of the study's outcomes. SJAH conducted the statistical analyses.

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COMPETING INTERESTS

The authors do not have any competing interests

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Prevalence and patterns of sensory processing behaviors in a large clinical sample of children with prenatal alcohol exposure

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ABSTRACT

Background: Atypical behavioral responses to sensation are reported in a large proportion of children affected by prenatal alcohol exposure (PAE). Systematic examination of symptoms across the fetal alcohol spectrum in a large clinical sample is needed to inform diagnosis and intervention.
Aims: To describe the prevalence and patterns of atypical sensory processing symptoms in a clinical sample of children with PAE.
Methods: Retrospective analysis of diagnostic clinical data from the University of Washington Fetal Alcohol Syndrome Diagnostic and Prevention Network (FASDPN). Participants were ages 3 through 11 years, had a diagnosis on the fetal alcohol spectrum, and Short Sensory Profile (SSP) assessment. The proportions of children categorized with definite differences on the SSP across selected clinical and demographic features were examined with chi-square analyses.
Outcomes: The sample consisted of 325 children; 73.2 % had SSP total scores in the definite difference range. Atypical sensory processing symptoms were significantly more prevalent among children with higher reported levels of PAE. The prevalence of atypical symptoms was comparably high across age, levels of diagnostic severity, and other prenatal/postnatal risks.
Conclusions: Results lend support for altered sensory processing as another domain of brain function affected by the teratogenic impact of PAE, guiding clinical work and research.

What this paper adds

Clinically significant sensory processing differences were highly prevalent in a large clinical sample of children with prenatal alcohol exposure (PAE) and outcomes consistent with fetal alcohol spectrum disorder. Findings corroborate previous reports of atypical sensory processing in smaller samples of children with PAE. Atypical sensory processing symptoms occurred in similarly high proportions across the full fetal alcohol spectrum, and across severity of key diagnostic features [central nervous system (CNS) function, facial features and growth)]. A higher prevalence of sensory processing differences was positively and significantly associated with children who had higher reported levels PAE. Findings lend support for the neurological processing of sensation as

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another neurobehavioral domain that is vulnerable to the teratogenic impact of PAE, and inform diagnosis, intervention and areas for future research.

1. Introduction

Fetal alcohol spectrum disorders (FASD) is an umbrella term that describes the full range of physical, cognitive and behavioral impairments associated with prenatal exposure to alcohol (PAE). FASDs are estimated to occur in at least 1% of the population with prevalence estimates varying based on geography and method of diagnosis (Astley, 2011; Astley, Bledsoe, Davies, & Thorne, 2017; Roozen et al., 2016; Sampson et al., 1997). Diagnoses such as fetal alcohol syndrome (FAS), partial FAS (PFAS), static encephalopathy/alcohol exposed (SE/AE) and neurobehavioral disorder/alcohol exposed (ND/AE) fall broadly under the umbrella of FASD (Astley, 2004). The central nervous system (CNS) impairments associated with these conditions and the subsequent impact of brain-based challenge on daily activities varies among individuals and across the fetal alcohol spectrum, as do the individual strengths, supports and protective factors that foster functional performance and promote resiliency throughout the lifespan (Astley, 2010; Streissguth et al., 2004).

The teratogenic effects of PAE on the central nervous system (CNS) that have functional implications are well-documented and include, but are not limited to, cognitive, motor, memory, executive function and communication impairments (Mattson, Bernes, & Doyle, 2019). Atypical responses to sensation are reported in a large proportion of children with FASD and are widely described clinically (Astley, 2010). However, a systematic examination of the prevalence and patterns of sensory processing symptoms across the fetal alcohol spectrum is lacking. Poorly modulated responses to sensation may be an indicator of CNS dysfunction; and understanding sensory processing patterns can provide insights into maladaptive and dysregulated behaviors and inform intervention (Dunn, Little, Dean, Roberston, & Evans, 2016). The recognition of sensory processing differences in this group of vulnerable and often underserved children has implications for diagnosis and intervention that have not been fully realized due to limited empirical evidence.

Sensory processing is a term used to describe the organization of sensation for use in daily life that involves a continuum of interactions between an individual's neurological thresholds and behavioral responses to sensation (Dunn, 2001, 2007). Behavioral patterns of hyper-responsiveness (e.g., discomfort, irritability) and hypo-responsiveness to sensation (e.g., not noticing or slowed response) have been described within and across sensory domains (e.g., tactile, auditory, vestibular). These atypical or poorly modulated responses to sensation may result in sensory processing or sensory integration disorders (Miller, Anzalone, Lane, Cermak, & Osten, 2007). Sensory processing and sensory integration disorders occur in 5–16 % of children in the general population (Ahn, Miller, Milberger, & McIntosh, 2004) and at much higher proportions (up to 80 %) among children with neurodevelopmental disabilities (Cheung & Siu, 2009). Atypical responses to sensation are well documented, for example, among children with autism spectrum disorder (Ben-Sasson, Hen et al., 2009; Ben-Sasson, Carter, & Briggs-Gowan, 2009; O'Donnell, Deitz, Kartin, Nalty, & Dawson, 2012) and are part of the Diagnostic and Statistical Manual of Mental Disorders (DSM–5) diagnostic criteria for this condition (American Psychiatric Association, 2013).

Previous studies report sensory processing differences among clinical samples of children with PAE including those meeting criteria for FASD (Abele-Webster, Magill-Evans, & Pei, 2012; Carr, Agnihotri, & Keightley, 2010; Franklin, Deitz, Jirikowic, & Astley, 2008; Jirikowic, Olson, & Kartin, 2008; Wengel, Hanlon-Dearman, & Fjeldsted, 2011). Children with FASD have been described as more reactive to touch, visual, and auditory stimuli compared to peers with typical development, and patterns of sensory-seeking behaviors and sensory hypo-responsivity also have been reported (Jirikowic, Olson, & Kartin, 2008). Sensory processing problems have been associated with increased problem behaviors (Franklin, Deitz, Jirikowic, & Astley, 2008) and poorer adaptive functioning among children with FASD (Carr, Agnihotri, & Keightley, 2010; Jirikowic, Olson, & Kartin, 2008). In combination with executive function impairments (behavior dysregulation), sensory processing problems in children with FASD are associated with higher levels of parenting stress among caregivers of children with FASD (Jirikowic, Olson, & Astley, 2012). Sensory processing differences appear to be pervasive among children with FASD and these behaviors have far-reaching impacts on daily life activities and family functioning.

Atypical responses to sensation are also described in prenatally alcohol-exposed animal models (Schneider, Moore, & Adkins, 2011). Schneider et al. (2008, 2011) reported an increased magnitude of withdrawal to tactile stimuli in association with PAE and reduced habituation to sensation in association with prenatal stress in a cohort of rhesus monkeys with prenatal alcohol and stress exposure. Further, symptoms of atypical sensory processing observed in the neonatal phase of development in these animal models were correlated with adult tactile sensory functions, suggesting developmental continuity of sensory processing symptoms (Schneider et al., 2017). Heightened reactivity to more aversive, or mildly painful stimuli has also been reported in rodent models (Rogers, Barron, & Littleton, 2004). The linkage of sensory processing disorder to PAE in animal models coupled with emerging evidence of associated neurophysiological changes and genetic influences (Schneider et al., 2008,2011,2017) bolster the need to more fully understand sensory processing disorders in children affected by PAE.

This study aimed to describe the prevalence of atypical sensory processing behaviors in a large clinical population of children systematically diagnosed with FASD, to explore risk factors associated with atypical sensory processing behaviors, and to explore sensory processing patterns across this population. The following research questions were asked:

1 What is the prevalence of atypical sensory processing behaviors among children with FASD?
2 Does the prevalence of atypical sensory processing behaviors vary by child characteristics [e.g., age, gender, level of alcohol exposure, FASD diagnosis, attention deficit hyperactivity disorder (ADHD)], or other prenatal or postnatal risk factors?

3 What are the patterns of sensory processing behaviors across sensory domains (e.g., tactile, auditory, vestibular) in children with FASD?

2. Materials and methods

2.1. Procedures

A retrospective analysis of clinical data from the Fetal Alcohol Syndrome Diagnostic and Prevention Network (FAS DPN) at the University of Washington was completed. The clinic has provided diagnostic evaluations for FASD, including FAS, since 1993. Patients of all ages (newborn to adult)newborn to adult are evaluated. The FAS DPN database currently contains over 2,000 fields of data (exposures and outcomes) on approximately 3000 patients with prenatal alcohol exposure. Data used for this study were collected with University of Washington Human Subjects approval and patient consent at the time of diagnosis.

All patients in the FAS DPN database were evaluated for FASD using the *4-Digit Diagnostic Code* (updated and coded according to criteria from the most current edition (Astley, 2004), an interdisciplinary approach to diagnosis guided by empirically validated criteria (Astley, 2004, 2013). The four digits of the FASD *4-Digit Diagnostic Code* reflect the magnitude of expression of the four key diagnostic features of FASD, in the following order: 1) growth deficiency, 2) FAS facial phenotype, 3) structural/functional CNS abnormalities, and 4) prenatal alcohol exposure. The magnitude of expression of each feature is ranked independently on a four-point Likert scale, with '1′ reflecting complete absence of the FASD feature and '4' reflecting a strong and classic presentation of the feature. Each Likert rank is specifically case defined. There are 102 4-Digit codes that fall broadly under the umbrella of FASD. These codes cluster into four clinically meaningful FASD diagnostic subcategories (Astley, 2004): fetal alcohol syndrome (FAS); partial FAS (PFAS); static encephalopathy/alcohol exposed (SE/AE); and neurobehavioral disorder/alcohol exposed (ND/AE).

2.2. Participants

Selected data from children who met the following study inclusion criteria were used: a) between 3 and 11 years old at time of diagnostic clinic visit, b) FASD diagnosis (including FAS or PFAS, SE/AE, or ND/AE), and c) completed Short Sensory Profile (SSP; McIntosh, Miller, Shyu, & Dunn, 1999). The FAS DPN began administering the SSP in the year 2000. Subjects with missing data on more than one-third of the items in any SSP domain were excluded.

2.3. Measures

2.3.1. Sensory processing behaviors

Short Sensory Profile (*SSP*: McIntosh et al., 1999) The SSP is a 38-item caregiver questionnaire that measures children's behavioral responses to sensation in daily life. The SSP is the short version of the longer 125-item Sensory Profile that is used for screening and research purposes (Dunn, 1999). The SSP examines behaviors in the sensory domains of Tactile Sensitivity, Taste/Smell Sensitivity, Movement Sensitivity, Under-responsive/Seeks Sensation, Auditory Filtering, Low Energy/ Weak, and Visual/Auditory Sensitivity. Caregivers report how frequently children respond in the way described by each item using a 5-point Likert scale (1 = almost always; 2 = frequently; 3 = occasionally; 4 = seldom; 5 = almost never). The SSP has high internal consistency for the total score (Cronbach's alpha = 0.96) and domain scores (Cronbach's alpha = 0.82 to 0.89). Lower raw scores indicate more atypical sensory processing behaviors. Raw scores are categorized as typical performance (scores at or above -1.0 standard deviation (SD) from the mean), probable differences (scores at or above -2.0 SD but lower than -1.0 from the mean) and 3) definite difference (scores below -2.0 SD from the mean).

2.3.2. FASD diagnosis and features

4-Digit Code FASD Diagnosis (FAS; PFAS; SE/AE; ND/AE). See full description above (Astley, 2004) and rankings for the following diagnostic features.

Growth Deficiency ('Growth Rank': 1 = none; 2 = mild; 3 = moderate; 4 = severe). This variable yields the first digit in the 4-Digit FASD Diagnostic Code and documents the magnitude of prenatal and/or postnatal growth deficiency (Astley, 2004).

FAS Facial Phenotype ('Face Rank': 1 = none; 2 = mild; 3 = moderate; 4 = severe). This variable represents the second digit in the 4-Digit FASD Diagnostic Code and documents the magnitude of expression of FAS facial phenotype defined by short palpebral fissure lengths, a smooth philtrum, and a thin upper lip (Astley, 2004).

CNS Likelihood of Structural Abnormality ('CNS Rank': 1 = unlikely; 2 = possible; 3 = probable; 4 = definite). This variable yields the third digit in the 4-Digit FASD Diagnostic Code. These four ranks document the increasing likelihood of CNS structural abnormality. Alcohol is a teratogen that interferes with the structural development of the fetal brain. This, in turn, can lead to abnormal function. The greater the dysfunction, the higher the probability of CNS structural abnormality (Astley, Aylward et al., 2009; Astley et al., 2009; Astley, 2013). The first three CNS Ranks document the severity of CNS dysfunction (Rank 1-no dysfunction; Rank 2-mild-to-moderate dysfunction; Rank 3-severe dysfunction). CNS Ranks 1–3 are based on brain function (executive function, memory, cognition, social/adaptive skills, academic achievement, language, motor, attention, and activity level) assessed by an interdisciplinary team using standardized psychometric tools. CNS Rank 4 documents the presence of direct evidence of CNS structural and/or neurological abnormalities (e.g., microcephaly, structural brain abnormalities, a seizure disorder of prenatal origin, or other hard neurological signs).

Prenatal Alcohol Exposure ('Alcohol Rank': 1 = confirmed absence of exposure; 2 = unknown exposure; 3 = confirmed exposure; level unknown or moderate; 4 = confirmed exposure; level high). Alcohol exposure is the fourth digit in the 4-Digit FASD Diagnostic Code, which is ranked according to the quantity, timing, frequency, and certainty of exposure during pregnancy. The ranking is determined by available records, maternal report or report from others who observed exposure. A diagnosis under the umbrella of FASD requires a confirmed PAE (Rank 3 or 4) with one exception-FAS. FAS requires the Rank 4 FAS facial phenotype which is so highly specific to (caused only by) PAE that the presence of the Rank 4 FAS facial phenotype offsets the need for an independently confirmed history of alcohol exposure.

2.3.3. Other risk factors

Attention Deficit Hyperactivity Disorder (ADHD) Diagnosis This variable documents a confirmed previous ADHD diagnosis from a qualified provider or as a result of the FAS DPN clinical assessment.

Other Prenatal Risk Rank (1 = no risk; 2 = unknown risk; 3 = some risk; 4 = high risk) (Astley, 2004). Other prenatal risk factors documented in the FAS DPN clinical database include poor prenatal care, pregnancy complications, presence of other syndromes/genetic abnormalities, and prenatal exposure to other substances (e.g., medications, tobacco, illicit drugs, and/or other teratogens). The 4-Digit Code ranks the magnitude of these other prenatal risks in a single composite measure labeled "Other Prenatal Risks Rank." Rank 4 is assigned when there is exposure to another teratogen (e.g., Dilantin) or when another syndrome or genetic condition is present (e.g., Down syndrome, Fragile X, etc.). Rank 3 is assigned to all other prenatal risks. The ranking is determined by available records and caregiver or other report on intake forms and/or clinical interview (Astley, 2004)

Other Postnatal Risk Rank (1 = no risk; 2 = unknown risk; 3 = some risk; and 4 = high risk) (Astley, 2004). Postnatal risk factors documented in the FAS DPN database include perinatal complications, number of home placements, physical and/or sexual abuse, neglect, and trauma. The 4-Digit Code ranks the magnitude of these other postnatal risks in a single composite measure labeled "Other Postnatal Risks Rank". Rank 4 is used to note severe postnatal circumstances that have been shown to have a significant adverse effect on development in most instances. Examples include physical or sexual abuse, multiple home placements, and severe neglect. Rank 3 is used to note conditions akin to those in Rank 4, but the circumstances are less severe. The ranking is determined by available records and caregiver or other report on intake forms and/or clinical interview.

2.4. Data analysis

SPSS version 19.0 (IBM Corp, 2010) and MedCalc for Windows, version 18.6 (MedCalc Software) were used to conduct the analyses. Descriptive statistics (means, standard deviations, proportions) were used to profile the demographic characteristics of the study population and SSP outcomes for the total score and seven domain scores. Relationships between the SSP total score and SSP domain score categories (typical performance, probable difference, and definite difference) and selected child demographics (age, gender, ADHD; co-occurring prenatal and postnatal risk factors) and FASD diagnosis and features were examined using chi-squared (χ^2) and Fisher's exact tests.

To further describe and explore sensory processing patterns, the proportion of item-level behaviors scored by caregivers as occurring always (100 % of the time or more) or frequently (about 75 % of the time) was analyzed. In addition, SSP outcomes were dichotomized into 2 categories: 1) typical performance and probable differences (scores at or above -2.0 SD from the mean) and 2) definite difference (below -2.0 SD from the mean) to explore domain scores and sensory over-responsiveness (SOR) characteristics. A "Sensory Over-Responsiveness (SOR)" score was calculated by combining SSP Tactile Sensitivity items (1–7), Taste/Smell Sensitivity items (8–11), Movement Sensitivity items (12–14), and Visual Auditory Sensitivity items (34–38 (Mazurek et al., 2013). Lower SOR scores indicate more sensory over-responsiveness. Finally, SSP domain scores and prevalence for children with FASD with and without ADHD were contrasted. All results were considered significant at 2-sided p-values of $< .05$. P-values for post-hoc analyses were exploratory and were not corrected for multiple comparisons and should be interpreted with appropriate caution.

3. Results

Records from 325 participants met study inclusion criteria; 43 were missing some SSP data. When item-level data were missing the average of the subject's remaining scores in the incomplete sensory domain was calculated and rounded to the closest whole number. This value replaced the missing score(s) in that domain. The adjusted item scores were rounded to the closest whole number. Clinical and sociodemographic characteristics for the total sample (n = 325) are presented in Table 1. Children had a range of diagnoses on the fetal alcohol spectrum, with the largest proportion diagnosed with ND/AE, followed by SE/AE and then FAS or PFAS (Table 1. The sociodemographic and clinical profile of this study sample is highly representative of the larger FAS DPN population of 3000 patients Astley, 2010).

3.1. Prevalence of atypical sensory processing behaviors

The proportion of children classified in each SSP category (typical performance, probable difference, definite difference) for each of the seven sensory domains and total score is shown in Fig. 1. Results indicated that 73.2 % of children in this sample were categorized with definite differences on the SSP total score. Differences were noted across all sensory domains with the highest proportions of definite differences in the domains of Auditory Filtering (81.8 %) and Under-responsive/Sensation Seeking (80.0 %). Definite differences in other domains associated with sensory over-responsiveness (SOR) were noted, but to a lesser extent (Fig. 1).

Table 1
Demographic and clinical profiles of 325 children with prenatal alcohol exposure.

Characteristic	N (valid %)
Gender	
Female	124 (38.2)
Male	201 (61.8)
Age at FASD Diagnosis (years)	
3-5.9	117 (36.0)
6-10.9	208 (64.0)
Mean (SD) Range	6.9 (2.1) 3.0–10.9
Race/Ethnicity	
Caucasian	157 (48.3)
African American	33 (10.2)
Native American/Canadian	23 (7.1)
Hispanic	14 (4.3)
Other (Including mixed race)	98 (30.2)
FASD Diagnosis[1]	
FAS	13 (4.0)
PFAS	19 (5.8)
SE/AE	96 (29.5)
ND/AE	197 (60.6)
Prenatal Alcohol Exposure: Alcohol Rank	
Rank 1: Confirmed absent	0 (0.0)
Rank 2: Unknown*	2 (0.6)
Rank 3: Confirmed/Amount moderate or unknown	160 (49.2)
Rank 4: Confirmed/Amount high	163 (50.2)
Other Prenatal Risks: Rank	
1: No risk	3 (0.9)
2: Unknown risk	12 (3.7)
3: Some risk	302 (92.9)
4: High risk	8 (2.5)
Postnatal Risks: Rank	
1: No risk	20 (6.1)
2: Unknown risk	3 (0.9)
3: Some risk	138 (42.5)
4: High risk	164 (50.5)
ADHD Diagnosis	
Yes	145 (46.9)
Caregiver at time of Diagnosis	
Biological parent	95 (30.2)
Other biological family member	44 (14.0)
Foster parent	65 (20.6)
Adoptive parent	126 (40.1)
Other	16 (5.1)

Notes. * 2 subjects with FAS had unknown prenatal alcohol exposures.
fetal alcohol spectrum disorder (FASD); fetal alcohol syndrome (FAS), partial FAS (PFAS), static encephalopathy/alcohol exposed (SE/AE); neurobehavioral disorder/alcohol exposed (ND/AE); attention deficit hyperactivity disorder (ADHD).

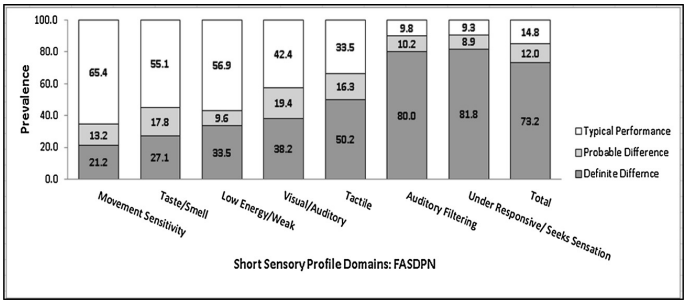

Fig. 1. Short Sensory Profile outcomes among the 325 children with prenatal alcohol exposure. Prevalence of typical performance, probable difference and definite difference across the seven SSP domains and total score.

Table 2
Associations between atypical sensory processing and clinical characteristics.

Characteristic	SSP Total Score		
	Typical/Probable Difference N (valid %) 87 (26.8)	Definite Difference N (valid %) 238 (73.2)	χ^2 (p-value)
Prenatal Alcohol Exposure			
Rank 3	54 (33.8)	106 (66.3)	8.2 (.004)
Rank 4	32 (19.6)	131 (80.4)	
FASD Diagnosis			
ND/AE	56 (28.4)	141 (71.6)	1.0 (.60)
SE/AE	22 (22.9)	74 (77.1)	
FAS/PFAS	9 (28.1)	23 (71.9)	

Notes. fetal alcohol spectrum disorder (FASD); fetal alcohol syndrome (FAS), partial FAS (PFAS), static encephalopathy/alcohol exposed (SE/AE); neurobehavioral disorder/alcohol exposed (ND/AE).

3.1.1. Sensory processing differences: FASD diagnostic characteristics

Atypical sensory processing symptoms (SSP total scores in the definite difference category) were significantly more prevalent among children with confirmed PAE at reportedly high levels (Alcohol Rank 4) than among those with confirmed PAE at unknown or reportedly lower levels (Alcohol Rank 3; Table 2). The prevalence of atypical sensory processing (SSP total scores in the definite difference range) was comparably high (72%–77%) across all FASD diagnoses (Table 2). The same pattern of distribution was observed across the four Growth Ranks, Face Ranks and CNS Ranks (data not shown). The prevalence of atypical sensory processing (SSP total scores in the definite difference range) was comparably high (67%–81.7%) across all ranks for growth, face and CNS (data not shown).

3.1.2. Sensory processing differences: child characteristics and risk factors

The prevalence of atypical sensory processing behaviors (SSP total scores in the definite difference range) did not vary significantly by age or clinical ranking of other prenatal risk factors or postnatal risk factors. Although a higher proportion of children with ADHD (73.1 %) had definite differences in the SSP total score than those without ADHD (68.9 %), differences in the total score were not statistically significant ($\chi^2 = 3.2$, $p = .07$). Significant differences by gender were found. Males were significantly more likely (78.1 %) to present with total scores in the definite difference range than females (65.3 %; $\chi^2 = 6.4$, $p = .011$).

3.2. Sensory processing patterns: exploratory analyses across behaviors and domains

Sensory processing patterns were further explored in three ways. Fig. 2 illustrates the proportion of item-level behaviors that were ranked by caregivers as occurring always (100 % of the time) or frequently (about 75 % of the time) within each of the seven sensory processing domains. Data show the frequency of specific sensory processing behaviors that are most problematic in daily life.

Sensory processing patterns were also compared by dichotomizing SSP total score outcomes into 2 categories, those with 1) typical performance and probable differences (scores at or above -2.0 SD from the mean) or 2) definite difference (at or below -2.0 SD from the mean) (see Fig. 3). Children with definite differences on the SSP total score were about twice as likely to have definite differences in both the Under-responsive/Seeks Sensation and Auditory Filtering domains as compared to those without. However, atypical behaviors in these two domains were the predominant symptoms in both groups. In contrast, the proportion of children with definite differences in the other sensory processing domains was consistently higher for those with definite differences on the SSP total score. For example, there was approximately a10-fold increase in the prevalence of definite differences in the domain of Movement Sensitivity; an 8-fold increase in the prevalence of definite differences in the domains of Tactile Sensitivity and Visual and Auditory Sensitivity; and a 4-fold increase in Taste/Smell Sensitivity.

These four sensory processing domain scores have items that comprise a score some have coined as the SOR score (Mazurek et al., 2013). Subsequently, we explored if the distribution of SOR scores differed between those who did and did not receive a total score in the definite difference range. We found the distribution of SOR scores was significantly different between groups (Area under the ROC curve (AUC) 0.935, $p < 0.0001$) and could be used to sort the groups with significant accuracy (81.5 % accuracy at the most accurate cut-point). The distribution of SOR scores differed significantly more between the two groups than either the Auditory Filtering score (AUC 0.860, significantly different than SOR, $p = 0.0092$) or the Under-responsive/Seeks Sensation score (AUC 0.870, significantly different than SOR, $p = 0.0141$).

Finally, because of the high prevalence of co-occurring ADHD in this sample and the atypical sensory processing behaviors that have been documented in other studies of children with ADHD (Panagiotidi, Overton, & Stafford, 2018), we also explored SSP patterns for the children with FASD in this sample who had ADHD compared to those who did not have ADHD (see Fig. 4). While the overall pattern across the seven domains in both groups was similar, definite differences in the Under-responsive/Sensation Seeking domain (89.0 % vs 76.2 %, respectively; $\chi^2 = 8.9$, $p = 012$) and Auditory Filtering domain (88.3 % vs 72.6 %, respectively; $\chi^2 = 11.9$ $p = 001$) were significantly more prevalent in children with co-occurring ADHD relative to those without ADHD, and males were significantly more likely to have a co-occurring diagnosis of ADHD (53.6 %) than females (35.7 %) ($\chi^2 = 9.3$, $p = .002$).

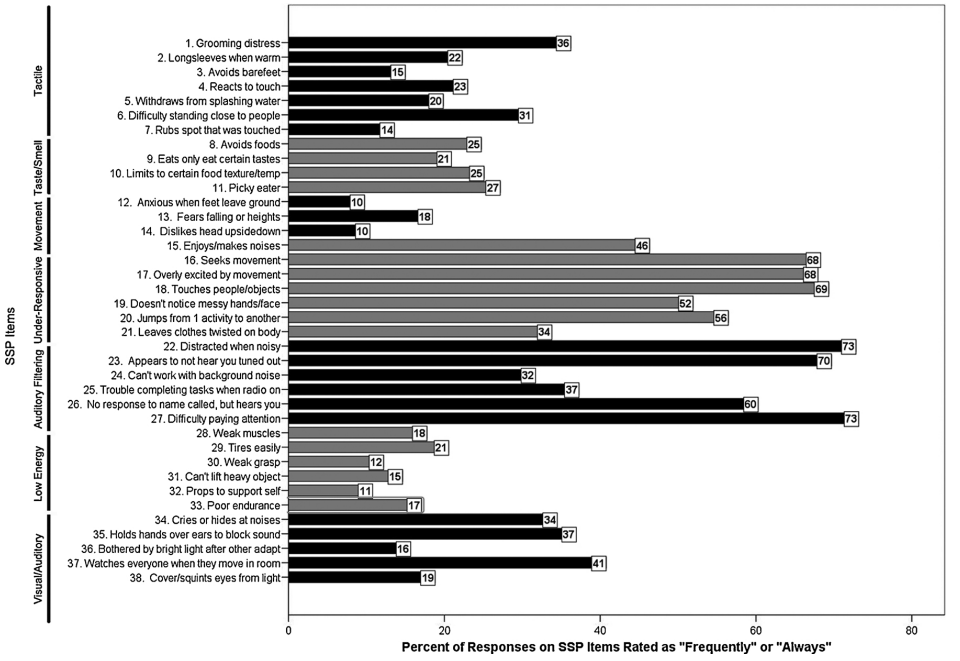

Fig. 2. Proportion of SSP item-level behaviors by domain ranked by caregivers as occuring Always (100% of the time or Frequently (about 75% of the time).

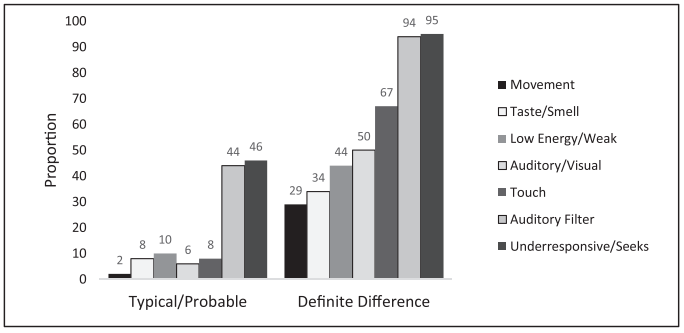

Fig. 3. Comparison of SSP domain scores by total score categories (definite difference vs. typical performance/probable difference. Bars reflect the proportion of the children with definite difference by SSP domain.

4. Discussion

This study is the first to report the prevalence of symptoms of sensory processing dysfunction in a large clinical sample of children with PAE and to demonstrate a significant positive association between prevalence of atypical sensory processing and PAE. Atypical sensory processing symptoms, as determined by total scores in the definite difference category of the SSP were prevalent in a high proportion (73.7 %) of children ages 3–11 years old, and significantly more prevalent among children with higher reported levels of confirmed PAE (Alcohol Rank 4) as compared to children with unknown or lower reported levels of confirmed PAE (Alcohol Rank 3). Males in this sample also had a significantly higher prevalence of sensory processing differences than females, but prevalence did not differ by other selected demographic or risk factors such as age, ADHD diagnosis, or level of other prenatal or postnatal risks. Results from this large clinical sample corroborate and strengthen findings that atypical sensory processing symptoms occur frequently

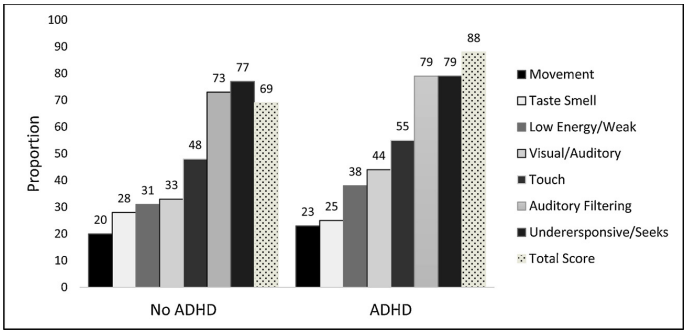

Fig. 4. Comparison of SSP domain scores for children with prenatal alcohol exposure who have co-occurring ADHD and those without ADHD.

among children with PAE, and that higher levels of PAE may induce more impairments in this domain of CNS functioning. While the latter finding needs replication and more research is needed to understand how PAE and sensory processing may be linked, direct associations between PAE and atypical sensory processing behaviors have been shown in alcohol-exposed animal models (Schneider et al., 2008, 2017).

The high prevalence of sensory processing differences across diagnoses on the fetal alcohol spectrum is consistent with prevalence estimates reported in previous studies of children with PAE that used smaller clinical samples (Abele-Webster et al., 2012; Carr, Agnihotri, & Keightley, 2010; Franklin, Deitz, Jirikowic, & Astley, 2008; Jirikowic, Olson, & Kartin, 2008). Even when using the conservative cut-off of -2.0 SD from the mean, almost three quarters (73.7 %) of the children with PAE had atypical responses to sensation. This prevalence falls at the higher end of the range of prevalence estimates (30%–80%) reported for other children with neurodevelopmental disabilities (Ben-Sasson, Hen et al., 2009; Ben-Sasson, Carter et al., 2009; Tomchek & Dunn, 2007). The item-level behaviors analyzed for this study shed light on how these behaviors affect participation in daily activities (e.g., distress during grooming; difficulty functioning with background noise, seeking all sorts of movement). Atypical sensory processing behaviors clearly occur and are a clinically significant problem among children with PAE.

As expected, atypical sensory processing behaviors were highly prevalent across the full fetal alcohol spectrum and severity of diagnostic features. Notably, impaired sensory processing occurred across all levels of CNS dysfunction that ranged from mild to moderate/severe. A striking new finding is that the prevalence of atypical sensory behaviors was significantly higher in children with higher levels of confirmed PAE. This association between PAE and atypical sensory processing behaviors in a large clinical sample lends support for sensory processing and integration as another CNS domain that is vulnerable to the teratogenic impact of alcohol. These clinical findings are substantiated by findings in animal models where less optimal sensory processing function (tactile over-responsivity and vestibular function) has been described in primates exposed to moderate levels of alcohol as compared to non-exposed controls (Schneider et al., 2008,2017, 2011).

Interestingly, the prevalence of atypical sensory processing behaviors in this clinical sample of children did not differ based on reported levels of other prenatal risks (e.g., pregnancy complications, other prenatal exposures, other syndromes/genetic abnormalities) or postnatal risks (e.g., physical/sexual abuse, neglect, trauma). The high prevalence of adverse childhood experiences reported in this clinical sample, coupled with findings by Schneider et al. (2017) that revealed a main effect of prenatal stress exposure in relation to atypical sensory processing in alcohol and stress exposed primate models prompted a post hoc analyses. The analyses explored whether more specific prenatal (i.e., exposure to tobacco or other illicit drugs, pregnancy complications, family history of developmental disorders, etc.) and postnatal (i.e., physical abuse, sexual abuse, neglect, multiple home placements) risks affected sensory processing outcomes. These analyses (data not shown) also did not reveal any significant relationships between SSP outcomes and specific risk factors. It is possible that in both analyses the presence of other prenatal and postnatal risk factors were not reported clinically with sufficient accuracy to detect true relationships with sensory processing outcomes.

Adversity and complex trauma have been implicated as risk factors that alter neurobehavioral development in areas that include self-regulation and sensory processing (van der Kolk, 2003). However, comparable systematic or descriptive clinical studies of sensory processing behaviors in children with complex trauma are limited for comparison. Purvis, Brooks, Cross, and Becker Razuri (2013) reported sensory processing deficits occurred in a small sample (n = 19) of adopted children 3–14 years old with histories of early deprivation or abuse. However, similar to other studies that describe the neurobehavioral implications of adverse childhood experiences and sensory processing in children, the presence (or absence of) PAE is not clearly accounted for (Fraser, MacKenzie, & Versnel, 2017; Rinne-Albers, van der Wee, Lamers-Winkelman, & Vermeiren, 2013). Future research that examines sensory processing in children with PAE who are also at high risk for other adverse childhood experiences such as trauma, abuse and neglect (Price, Cook, Norgate, & Mukherjee, 2017) must account for the potential interaction of both PAE as a teratogen and cumulative environmental risk factors as they collectively may alter developmental outcomes and trajectories.

Males in this sample had a significantly higher prevalence of sensory processing differences than females, but prevalence estimates across the SSP total score did not differ by other selected demographic factors (age or ADHD diagnosis). Gender differences,

developmental implications and the overlap of sensory processing symptoms with other neurobehavioral characteristics (e.g., inattention) are noteworthy because they have been examined in other groups of children with sensory processing problems and neurodevelopmental disabilities, but findings are mixed and inconclusive (Ghanizadeh, 2011; Lane, Reynolds, & Thacker, 2010; Miller, Nielsen, & Schoen, 2012; Panagiotidi et al., 2018). Specific to children with FASD, Abele-Webster et al. (2012) also reported differences in the domains of Under-responsive/Sensation Seeking and Auditory Filtering to be the most prevalent among a small clinical sample (n = 26) of children with FASD, but found only weak correlations between sensory processing and attention problems as measured by the Connors Parent Rating Scales-Revised (1997). More recently, SSP Auditory Filtering behaviors were extensively examined by McLaughlin et al. (2019) as a proxy for listening behaviors among children with FASD. Listening problems, attributed to suprathreshold auditory processing deficits, were highly prevalent across all diagnosis on the fetal alcohol spectrum and occurred in the absence of hearing loss. Auditory Filtering differences were also significantly correlated with age and ADHD.

These relationships and potential shared mechanisms underlying sensory processing impairments are being investigated through biobehavioral studies of children with and without clinical sensory processing deficits. For example, Davies, Chang, and Gavin (2009) measured auditory event-related potential (ERP) responses using electroencephalography (EEG) in children with sensory processing disorders, children with typical development and adults. They reported differences in the maturational trajectories of sensory gating, the brain's capacity to regulate sensitivity to sensory stimuli, between children with and without clinical sensory processing disorders (SPD). The children with SPD also showed a diminished ability to filter repeated auditory input and did not selectively regulate sensitivity to sensory stimuli. Owen et al. (2013) reported disrupted white matter microstructure integrity examined through diffusion tensor imaging (DTI) in a sample of 8–11 year-old males with and without SPD. The differences noted in posterior cerebral tracts were strongly correlated with behavioral measures of atypical sensory processing and integration. The authors concluded that abnormal white matter may be a biomarker for children with SPD with potential to distinguish this disorder from other clinical conditions such as autism and ADHD. Neuroimaging and neurophysiological studies of sensory processing need replication in children with FASD to corroborate behavioral findings, disentangle co-morbid symptoms, and examine these brain-behavior relationships in the presence of PAE as a teratogen.

The predominant patterns of differences in Under-responsive/Sensation Seeking and Auditory Filtering domains coupled with differences, but to a lesser degree, in domains that represent sensory over-responsiveness are congruent with profiles reported in previous studies of children with FASD (Abele-Webster et al., 2012; Carr, Agnihotri, & Keightley, 2010; Franklin, Deitz, Jirikowic, & Astley, 2008). The distinction of subtypes for children with PAE is beyond the scope of the present study and limited by the use of the SSP, however, the robust patterns of under-responsive/sensation seeking tendencies are notable, but wider ranging differences (21%–50%) in sensory domains that represent sensory-over-responsiveness, suggest more analyses of subtypes is an important area of future study. Our exploratory analysis also suggests that the presence of more frequent sensory-over responsive behaviors may potentially differentiate atypical sensory processing from other overlapping symptoms in this population, such as inattention. Clinical sensory processing subtypes and their relation to behavior patterns as well as neurobehavioral and diagnostic characteristics within and between different populations of children are important areas of focus of current research (Little, Dean, Tomchek, & Dunn, 2017; Little, Dean, Tomchek, & Dunn, 2018; Miller, Schoen, Mulligan, & Sullivan, 2017).

Because of the overarching interest in sensory behaviors and sensory processing patterns between different diagnostic groups and the lack of previous studies that include a comparison group of children with FASD, exploratory post hoc contrasts were made using data from a previous study that reported SSP outcomes for children of similar age on the autism spectrum. Fig. 5 shows contrasts between outcomes across the three SSP classification categories of typical, probable and definite differences using outcomes from 42 children with ASD (O'Donnell et al., 2012) in comparison to the current sample of children with FASD.

Notably, the proportion of sensory processing definite differences for the total score and five out of seven domain scores were higher for children with FASD compared to children with ASD. Children with FASD showed more atypical behaviors in the definite difference category across all domains except for the Taste/Smell domain where the children with ASD had a greater proportion of definite differences; and the Movement Sensitivity domain, where the proportion of definite differences was comparable. Results reveal specific sensory domains (e.g., oral sensory processing) that may be different, as well as sensory behaviors that may overlap between children with FASD as compared to children with ASD-a group with well-documented sensory processing differences (Ben-Sasson, Hen et al., 2009; Ben-Sasson, Carter et al., 2009; Caminha & Lampreia, 2012) and diagnostic criteria that includes atypical sensory symptoms. While these exploratory analyses must be interpreted with caution, findings further demonstrate the need to include children with FASD in systematic comparisons of sensory processing with other clinical groups. Systematic comparisons can enrich larger scale research efforts that aim to improve the early identification of sensory processing impairments in children at-risk; inform individualized, targeted interventions; and examine shared neurological mechanisms underlying sensory processing disorders (Little et al., 2018).

4.1. Limitations

One study limitation is the use of caregiver reported outcome to measure sensory processing differences. Caregivers may be biased in their reporting of symptoms. However, caregiver report is an accepted clinical means of measuring ecologically valid behaviors that reflect daily function and responses in different environments. Likewise, the SSP is a short version of a more comprehensive questionnaire. However, the SSP has adequate to good psychometric reliability and validity and has been used extensively in research (Tomchek & Dunn, 2007). Because this was a retrospective study, our data do not reflect the use of the newer and perhaps more refined tools that can measure more and different dimensions of sensory processing (Jorquera-Cabrera, Romero-Ayuso, Rodriguez-Gil, & Triviño-Juárez, 2017). The precise measurement of sensory processing for assessment and intervention purposes remains a

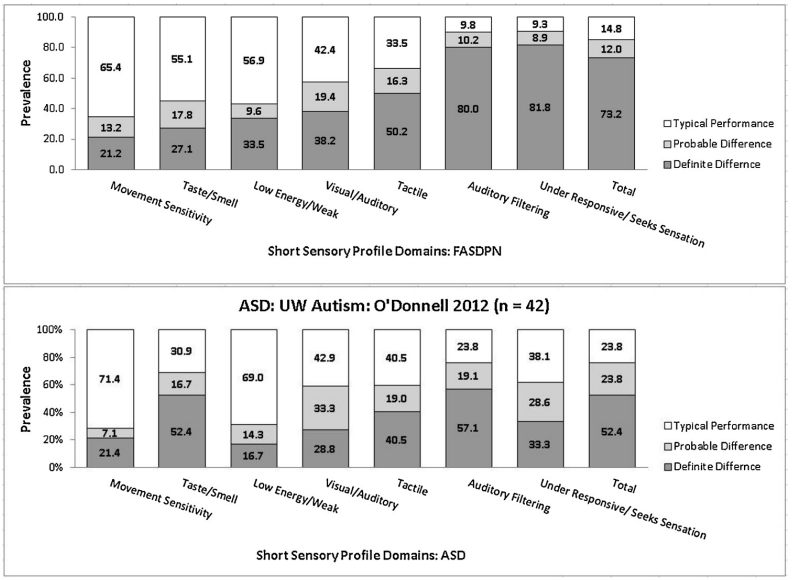

Fig. 5. Comparison of SSP outcomes among A) the 325 children with FASD in the current study and B) 42 children with autism spectrum disorder in a previous published study (O'Donnell et al., 2012). Proportion of of typical performance, probable difference and definite difference across the seven SSP domains and total score.

research and clinical priority, and combined approaches that use questionnaires, direct clinical observation and performance-based assessments are recommended Tvassoli et al. (2019).

5. Conclusion

Results demonstrate that clinically significant sensory processing differences are highly prevalent in a large clinical sample of children with PAE and diagnostic outcomes on the fetal alcohol spectrum. Higher prevalence of sensory processing differences among children with higher levels of PAE suggests that neurological processing of sensation may be vulnerable to the teratogenic impact of PAE. From a clinical standpoint, this reinforces that sensory processing behaviors warrant attention in diagnostic assessments since they occur across the full spectrum of diagnosis. The recognition of sensory processing differences is also an important source of data to inform interventions that can help reframe challenging behaviors, provide positive behavioral supports and accommodations and help tailor environments that enable successful participation in home, school and community.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ridd.2020.103617.

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What proportion of the brain structural and functional abnormalities observed among children with fetal alcohol spectrum disorder is explained by their prenatal alcohol exposure and their other prenatal and postnatal risks?

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Abstract

Background: Individuals with prenatal alcohol exposure (PAE) often present with a myriad of other prenatal (e.g. exposure to tobacco and other illicit drugs, poor prenatal care) and postnatal risk factors (e.g. multiple home placements, physical/sexual abuse, low socio-economic status)-all of which are likely contributing to their adverse outcomes.

Methods: A comprehensive neuropsychological battery, coupled with magnetic resonance imaging, was administered to children with fetal alcohol spectrum disorders (FASD) in 2009. Study participants diagnosed with FASD by the University of Washington using the FASD 4-Digit Code were compared to typically-developing peers with no PAE. Data from this MRI study were used to explore the proportion of variance in brain structural and functional abnormalities explained by PAE and 14 other prenatal and postnatal risk factors.

Results: PAE was the dominant risk factor explaining the largest proportion of variance in regional brain size (total brain, frontal lobe, caudate, hippocampus and corpus callosum) and brain function (intellect, achievement, memory, language, executive-function, motor, adaptation, behavior-attention and mental health symptoms). Other prenatal and postnatal risk factors were 3 to 7-fold more prevalent than in the general population. Individually, each risk factor explained a statistically significant, but smaller proportion of variance in brain outcome compared to PAE. In combination, the proportion of variance explained by the presence of multiple prenatal and postnatal risks rivaled that of PAE.

Conclusion: A better understanding of the impact other prenatal and postnatal risk factors have on the neurodevelopmental outcomes of individuals with FASD can inform more effective prevention and intervention strategies.

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Introduction

Individuals with prenatal alcohol exposure (PAE) often present with a multitude of other prenatal (e.g. exposure to tobacco and other illicit drugs, poor prenatal care, premature birth) and postnatal risk factors (e.g. multiple home placements, physical/sexual abuse, low socio-economic status (SES) [1,2]. Each of these risks individually is known to contribute to adverse neurodevelopmental outcomes [3-9].

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To date, little research has examined the combined impact of these other prenatal and postnatal exposures on the neurodevelopmental outcomes of children with PAE. Interactions between PAE and prenatal cocaine exposure have been documented in a few studies [10-12]. Streissguth et al., [13] documented more impaired outcomes among individuals with FASD that experienced longer versus shorter durations of adverse postnatal experiences (abuse, violence, neglect). In a literature review, Price et al., [14] identified five studies that investigated the combined impact of trauma in children with PAE. In one of these studies, children with both PAE and trauma were more likely to have deficits in language, attention, memory, intelligence and more severe behavioral problems than children with only one of these adverse exposures [15]. Most recently, Uban et al., [16] assessed the impact of socioeconomic status (SES) on neurostructural development in children with and without PAE. As anticipated, typically developing youth without PAE exhibited increased subcortical volumes with increased SES. But unexpectedly, SES-brain associations were not observed among the youth with PAE.

Two key challenges to researching the adverse impacts of PAE and other prenatal and postnatal risk factors on neurodevelopment are 1) finding reliable documentation of these adverse exposures and experiences; and 2) having access to a study population that have all had the same comprehensive, standardized neuropsychological battery of assessments and MR imaging protocols. PAE along with other prenatal and postnatal risks are typically recorded in past medical, legal and social service records; records that are routinely obtained by FASD diagnostic clinics in preparation for a FASD diagnostic evaluation. Review and documentation of these other risks has always been a priority with the FASD 4-Digit Code, a systematic, validated diagnostic system. These risk factors are formally recorded in the FASD 4-Digit Code Diagnostic Form [17] and ranked on 4-point Likert scales (Prenatal Rank and Postnatal Rank) just like the growth, face, brain and alcohol components of the FASD 4-Digit Code. But FASD diagnostic clinics rarely have the ability to validly administer a single, standardized, comprehensive battery of neuropsychological assessments to all patients. Many factors come into play when selecting the most appropriate battery for an individual patient (their age, clinical presentation, previous participation in neuropsychological assessments, etc.). Comprehensive, standardized neuropsychological assessment batteries and MRI imaging protocols are the mainstay of controlled research studies, not diagnostic clinics.

The present study sought to capitalize on the combined strengths of our clinical and research programs. In 2009, a comprehensive FASD neuropsychological-magnetic resonance imaging study was completed at the University of Washington FAS Diagnostic & Prevention Network (FASDPN) [18-21]. Patients previously diagnosed across the full continuum of FASD were enrolled in the study. The combination of clinical and research protocols produced a study population with the full complement of exposure and outcome measures necessary to explore the proportion of variance in brain structural and functional abnormalities explained by PAE and other prenatal and postnatal risk factors. A better understanding of the impact other prenatal and postnatal risk factors have on the neurodevelopmental outcomes of individuals with FASD can inform more effective primary prevention and intervention strategies.

Research Methodology

Subjects and study groups

The current study is a retrospective exploratory analysis of data collected from a 2009 neuropsychological and magnetic resonance imaging (MRI) study [18-21] comparing central nervous system (CNS) structural and functional outcomes between children with FASD and typically developing peers with confirmed absence of PAE. In the original 2009 study, three FASD groups (defined below) were selected from among 1,200 patients previously diagnosed by an interdisciplinary team in the WA State FAS Diagnostic & Prevention Network (FAS DPN) of clinics using a comprehensive, validated diagnostic system called the FASD 4-Digit Code [17,22,23]. Briefly, the 4 digits of the FASD 4-Digit Code reflect the magnitude of expression of the 4 key diagnostic features of FASD, in the following order:

1. Growth deficiency,
2. FAS facial phenotype,
3. CNS structural/functional abnormalities, and
4. PAE

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The magnitude of expression of each feature was ranked independently on a 4-point Likert scale, with 1 reflecting complete absence of the FASD feature and 4 reflecting a strong "classic" presence of the FASD feature. Each Likert rank is specifically case defined (Figure 1). 4-Digit Codes range from 1111 to 4444. Each 4-digit diagnostic code falls into 1 of 22 unique clinical diagnostic categories (labeled A through V). Seven of the 22 diagnostic categories (4-Digit Categories A–C and E–H) fall under the umbrella of FASD (A. FAS/ Alcohol Exposed, B. FAS/Alcohol Exposure Unknown, C. Partial FAS/Alcohol Exposed, E & F. Static Encephalopathy/Alcohol Exposed, and G & H. Neurobehavioral Disorder/Alcohol Exposed).

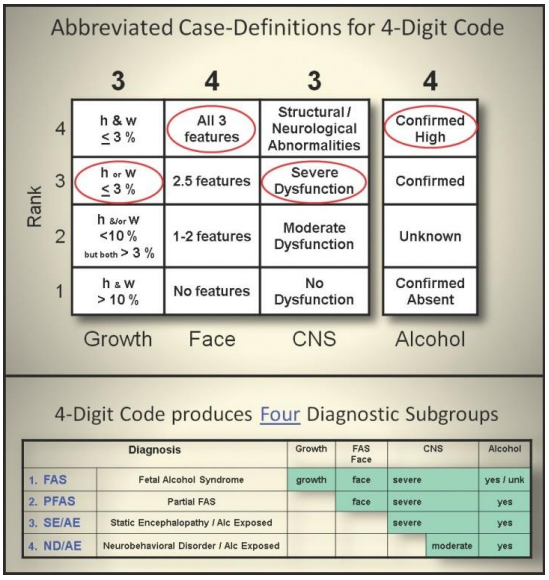

Figure 1. Abbreviated case-definitions of the FASD 4-Digit Code [17,23].
The 4-Digit Code 3434 is one of 12 Codes that fall under the diagnostic category FAS. The 4-Digit Code produces four diagnostic subgroups under the umbrella of FASD: FAS, PFAS, SE/AE, and ND/AE. Abbreviations: Alc alcohol; CNS central nervous system; h height; w weight; % percentile

The control population in the original 2009 study was selected from a large cohort of children enrolled at birth in a University of Washington study of typical development conducted through the Department of Speech and Hearing Sciences. This registry has been maintained over the years to serve as a source of typically developing controls for studies throughout the University. With the enrollment of each child in the FAS/PFAS group, a child matched on age (within 6 months), gender, and race was randomly identified and invited to enroll from the eligible SE/AE, ND/AE and Control populations.

The enrollment procedure for the original 2009 study produced a sample of 81 children. The age range (8 to 15.9 years) included the broadest age range of children that could be administered a comparable psychometric assessment battery and be reasonably capable of participating in the MR scanning. Each of the four study groups had 16-24 subjects successfully balanced on age, gender, and race. The 61 children with FASD in the original study were highly representative of the entire clinic sample of 2,828 from which they were drawn [1].

The diagnostic features specific to each study group were as follows:

1. Children in Group 1 had a 4-Digit diagnosis of FAS or Partial FAS (FAS/PFAS)/ Alcohol Exposed (e.g. 4-Digit Diagnostic Categories A,B,C: with Growth Ranks 1-4, Face Ranks 3-4, CNS Ranks 3 and/or 4, Alcohol Ranks 3-4). In summary, children in Group 1 had severe cognitive/behavioral dysfunction and the FAS facial phenotype.

2. Children in Group 2 had a 4-Digit diagnosis of Static Encephalopathy / Alcohol Exposed (SE/AE) (e.g. 4-Digit Diagnostic Categories E,F: with Growth Ranks 1-4, Face Ranks 1-2, CNS Ranks 3 and/or 4, Alcohol Ranks 3-4). In summary, children in Group 2 had severe cognitive/behavioral dysfunction, comparable to Group 1, but did not have the FAS facial phenotype.

3. Children in Group 3 had a 4-Digit diagnosis of Neurobehavioral Disorder / Alcohol Exposed (ND/AE) (e.g. 4-Digit Diagnostic Categories G, H: with Growth Ranks 1-4, Face Ranks 1-2, CNS Rank 2, Alcohol Ranks 3-4). In summary, children in Group 3 had PAE comparable to Groups 1 and 2, but in comparison to Groups 1 and 2 had only mild to moderate cognitive/behavioral dysfunction, and did not have the FAS facial phenotype.

4. Children in Group 4 (Typically Developing Controls / No Alcohol Exposure) were selected based on parental report that the child was typically developing, and no PAE (e.g. 4-Digit Diagnostic Category V: with Growth Ranks 1-2, FAS Face Ranks 1-4, CNS Ranks 1-2, Alcohol Rank 1). In

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summary, these were non-exposed, average to high functioning controls.

Socio-demographic and clinical assessment

In the original 2009 study a comprehensive sociodemographic and health/medication history of each child was obtained by parent interview and record review. Information included birth data, growth, and all prenatal and lifetime exposures and adverse events. For subjects with FASD, most information was obtained at the time of their FASD diagnostic evaluation and recorded on the 4-Digit Code FASD Diagnostic Form [17].

Measures of PAE

The following measures of maternal alcohol consumption were collected retrospectively, with a focus on two time points (just before pregnancy and during pregnancy): a) average and maximum number of drinks per drinking occasion, b) average number of drinking days per week, c) type(s) of alcohol consumed (beer, wine, liquor), and d) trimester(s) of exposure.

Other prenatal and postnatal risk factors

Measures of other prenatal and postnatal adverse exposures and experiences were collected from a caregiver interview and/or review of records. Prenatal risks included: maternal use of tobacco, marijuana, cocaine, any illicit drugs and no prenatal care (all measured on a yes/no scale). While illicit drugs other than marijuana and cocaine were reported, the prevalence of each individual drug was too low in this study population to include as separate risk factors. Postnatal risks included: not living with either birth parent, number of foster placements, physical abuse, sexual abuse, SES of current caregiver (e.g. years of education attained, occupation prestige, and gross annual family income level). All SES measures were based on the subject's current primary caregiver participating in the study. Education and occupation were codified in accordance with the Hollingshead Four-Factor Index of SES [24] as follows. The parent ' s education was rated on a 7-point scale with 1 equal to less than a 7th grade education; 4 equal to a high school education and 7 equal to graduate/ professional training. The parent ' s occupational code was rated on a 9-point scale from 1 equal to farm laborers, menial service workers, students, housewives; 6 equal to technicians, semi-professionals, small business owners, to 9 equal to higher executive, proprietor of large businesses, major professionals. The scale score for education is multiplied by a weight of three; the scale score for occupation is multiplied by a weight of 5. Annual income was coded < $50,000 reflecting roughly twice the U.S. Health and Human Services Poverty Guidelines for a family of four in 2009 [25].

All children had a standardized digital facial photograph taken at the time of enrollment in the original 2009 study. The facial photographs were analyzed using the FAS Facial Analysis Software [26] to generate two measures of the magnitude of expression of the FAS facial phenotype: 1) the 4-Digit Code Facial Rank (1 to 4) [23] and 2) the continuous FAS facial D-score [27]. The D-score documents the severity of the FAS facial phenotype on a continuous scale. The higher the D-score, the more FAS-like the facial phenotype. A D-score > 0.8 is equivalent to a Rank 4 FAS facial phenotype.

Neuropsychological / Psychiatric assessments

In the original 2009 study, a comprehensive, standardized neuropsychological battery was administered to each child and their primary caregiver by a psychologist masked to group assignment (Table 1). Based on an extensive review of the prior literature, the assessment battery was designed to capture the domains of potential neuropsychological deficit and mental health conditions seen as the result of the typically diffuse brain damage arising from alcohol teratogenesis [28-30]. Key outcome measures (composite and subtest scores) from the battery of assessments were selected in the original study to represent the different domains of deficit (Figure 2). These same outcome measures served as the primary dependent variables for brain function in the current study [31-75].

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Table 1. Assessment battery administered to the four study groups.

Soft Neurological Signs	Quick Neurological Screening Test II (QNST-II) [60]
General Intellectual Function	Wechsler Intelligence Scale for Children-Third Edition (WISC-III) [33]
Academic Achievement	Wechsler Individual Achievement Test (WIAT) Basic Reading subtest) [61]
	KeyMath Revised/NU: A Diagnostic Inventory of Essential Mathematics [62]
Visuospatial Skills, Visual Memory, and Organization	Beery Buktenica Developmental Test of Visual-Motor Integration (VMI) [63]
	Rey Complex Figure Test (RCFT) [64]
Executive Function	Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test [65]
	Delis-Kaplan Executive Function System (D-KEFS) Tower Test [65]
	Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference Test [65]
	Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency Test: Standard [65]
	Wisconsin Card Sorting Test: Computer Version 3 (WCST) Research Edition [66]
Verbal Memory	California Verbal Learning Test-Children's Version (CVLT-C) [67]
Attention	Integrated Visual and Auditory Continuous Performance Test (IVA CPT) [68]
Receptive and Expressive Language	Test of Language Development-Intermediate: Third Edition (TOLD-I:3) [69] • Sentence Combining subtest (subjects aged 8 to 10 years)
	Test of Language Competence-Expanded Edition (TLC-1-Expanded) Level 1 [70] • Oral Expression: Recreating Speech Arts subtest (subjects aged 8 to 9 years)
	Test of Language Competence-Expanded Edition (TLC-2-Expanded) Level 2 [70] • Oral Expression: Recreating Sentences subtest (subjects aged 10 to 15.9 years)
	Test of Word Knowledge (TOWK) [71] • Conjunctions and Transition Words subtest (subjects aged 11 to 15.9 years)
Adaptive Behavior	Vineland Adaptive Behavior Scales (VABS) Interview Edition, Survey Form[72]
Behavior Problems and Social Competence	Child Behavior Checklist for Ages 6-18 (CBCL/6-18) [73]
Caregiver Report of Behaviors Related to Executive Function	Behavior Rating Inventory of Executive Function (BRIEF) [74]
Psychiatric Conditions	Computerized Diagnostic Interview Schedule for Children: Parent Form (C-DISC) [75]

Magnetic resonance evaluation

The MRI components of this study are reported separately [19]. Briefly, all scans were acquired using a General Electric 1.5 Tesla scanner in the Diagnostic Imaging Sciences Center at the University of Washington. MRI was used to measure the size (volumes and/or midsagittal areas) of the following structures: total brain, frontal lobe, caudate, putamen hippocampus, corpus callosum, and cerebellar vermis. These outcomes served as the primary dependent variables for brain structure.

Statistical analyses

Descriptive statistics (means, SDs, proportions) were used to summarize the sociodemographic and clinical profiles of the four study groups (Table 1). For comparisons between groups, chi-square was used for categorical variables and ANOVA was used for continuous variables. When ANOVA was employed, the overall f- statistic was used to test if differences existed among the four group means. When the overall f-statistic was statistically significant, the Duncan post hoc range test was used to identify which group means differed. The

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Duncan test makes pairwise comparisons using a stepwise procedure. Means are ordered from highest to lowest, and extreme differences are tested first. The Duncan test identifies homogeneous subsets of means that are not different from one another. For example, when the mean head circumference was compared across the 4 study groups, the outcome was depicted 1,23,4 (group 1 was significantly smaller than groups 2 and 3, and group 4 was significantly larger than groups 1, 2 and 3. SPSS [31] linear regression with forward entry (probability of F to enter <0.05) was used in this exploratory analysis to identify which risk factor(s) explained a statistically significant proportion of the variance in CNS structural and functional outcomes. With forward entry, independent variables are added to the equation one at a time. At each step, the variable not in the equation with the smallest probability of F is entered if the value is smaller than .05. The order in which independent variables are entered into the equation provides insight about the quality of the predictor variables. Separate regressions were conducted for each CNS brain region and each neuropsychological measure within each functional domain (Figure 2). These separate regressions were conducted, in part, to explore if similar patterns of risk factors explained the different neuropsychological outcomes within a domain of function (e.g. were similar patterns of risk identified across the five WISC-III subtests within the General Intellectual Function domain) (Figure 2). Also of interest was whether similar patterns of risk were identified between brain regions and functions often attributed to those brain regions (e.g. hippocampus and memory, caudate and cognition). Only cases with valid data across all variables were included in each regression analysis (SPSS missing = list wise procedure). All regressions met the following goodness of fit and collinearity parameters: dependent variables normally distributed; independent variables: tolerance >0.1, Variance Inflation Factor <10, variance decomposition proportions: no two variables >0.90 and Condition Index <50. Partial and standardized residual plots were used to validate assumptions of normality, linearity and equality of variances. The proportion of variation in the dependent variable (brain region sizes and neuropsychological assessment scores) attributable to each risk factor is reported as the adjusted R^2. The adjusted R^2 is a modified version of R^2 that has been adjusted for the number of predictors in the model. P-values were not adjusted for multiple comparisons in this exploratory analysis, thus should be interpreted accordingly.

Results

Study population

Of the 81 subjects enrolled in the original MRI study, 50 presented with complete data across all independent and dependent variables needed for this current study. Although presence or absence of PAE was reliably documented for all subjects; more detailed information such as quantity, frequency, and duration of PAE was only available on 53 of the 65 alcohol-exposed subjects. This is not atypical, as accurate, detailed alcohol histories are frequently unavailable on patients presenting to a FASD diagnostic clinic. The regression analyses described below confirmed that the more detailed measures of quantity, frequency and timing of PAE (not just the presence or absence of PAE) were necessary to detect the correlations between PAE and brain outcomes. It is for this reason the study sample was restricted to those with this level of detail available. All controls had a reported absence of PAE per birth mother report. This subset of 50 subjects (11 FAS/PFAS, 12 SE/AE, 11 NE/AE and 16 Controls) (Table 2) was highly representative of the larger study group of 81 subjects in the original 2009 study [19,20] as well as the entire clinical population of 2,828 patients evaluated to date in the FASDPN clinic [1,32] from which they were selected.

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Table 2. Sociodemographic and FASD 4-Digit Diagnostic Code profiles of the four study groups.

Characteristic	Groups				Statistics		
	1. FAS/PFAS[A,B]	2. SE/AE	3. ND/AE	4. Control	ANOVA		Chi[2]
					Overall	PostHoc	Chi
	N = 11	N = 12	N = 11	N = 16	F (p)[C]	Duncan	(p)
Gender: female, n (%)	5 (45.5)	9 (75.0)	6 (54.5)	8 (50.0)			2.5 (.48)
Age in years at enrollment, mean (SD)	12.9 (2.4)	12.5 (2.7)	11.8 (2.7)	12.4 (2.7)	.33 (.81)		
Race, n (%)							
Caucasian	6 (54.5)	4 (33.3)	7 (63.6)	13 (81.3)			6.1 (.11)[D]
African American	3 (27.3)	3 (25.0)	3 (27.3)	2 (12.6)			
Native American	2 (18.2)	5 (41.7)	1 (9.0)	0 (0.0)			
Asian	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)			
Growth Rank, 4-Digit Code, n (%)							
1. None	4 (36.4)	9 (75.0)	7 (63.6)	15 (93.7)			10.5 (.01)[E]
2. Mild	2 (18.2)	2 (16.7)	3 (27.3)	1 (6.3)			
3. Moderate	4 (36.4)	0 (0.0)	0 (0.0)	0 (0.0)			
4. Severe	1 (9.1)	1 (8.3)	1 (9.1)	0 (0.0)			
Face Rank, 4-Digit Code, n (%)							
1. None	0 (0.0)	3 (25)	3 (27.3)	10 (62.5)			
2. Mild	0 (0.0)	9 (75)	8 (72.7)	6 (37.5)			
3. Moderate	3 (27.3)	0 (0.0)	0 (0.0)	0 (0.0)			
4. Severe [F]	8 (72.7)	0 (0.0)	0 (0.0)	0 (0.0)			
FAS facial D-score [G], mean (SD)	1.16 (1.0)	-0.6 (1.0)	-0.8 (0.7)	-1.5 (0.9)	17.8 (.000)	1,23,34	
CNS Ranks 1-3, 4-Digit Code, Functional impairment level, n (%)							
1. None	0 (0.0)	0 (0.0)	0 (0.0)	16 (100)			
2. Moderate	0 (0.0)	2 (16.7) [H]	11 (100)	0 (0.0)			
3. Severe	11 (100)	10 (83.3)	0 (0.0)	0 (0.0)			
CNS Rank 4, 4-Digit Code Structural/Neurologic Abnormality, n (%)	10 (90.9)	3 (25.0)	0 (0.0)	0 (0.0)			10.1 (.001)[I]
Current OFC percentile, mean (SD)	10.9 (29.2)	51.6 (34.6)	53.6 (8.7)	82.7 (18.1)	19.7 (.000)	1,23,4	
Microcephaly (OFC ≤ -2 SD), n (%)	10 (90.1)	2 (16.7)	0 (0.0)	0 (0.0)			12.7 (.000)[J]
Alcohol Rank, 4-Digit Code, n (%)							
1. Confirmed absent	0 (0.0)	0 (0.0)	0 (0.0)	16 (100)			
2. Unknown exposure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
3. Confirmed: Level moderate or Unk	1 (9.1)	1 (8.3)	2 (18.2)	0 (0.0)			
4. Confirmed: Level high	10 (90.9)	11 (91.7)	9 (81.8)	0 (0.0)			
Alcohol prior to pregnancy							
Days/week, mean (SD)	5.3 (1.8)	4.4 (2.0)	5.4 (2.1)	0.9 (1.0)	20.8 (.000)	123,4	
Most drinks/occasion, mean (SD)	23.1 (24.8)	23.0 (28.3)	13.5 (7.7)	1.7 (1.5)	4.2 (.01)	123,4	
Alcohol during pregnancy							
Days/week, mean (SD)	5.5 (1.7)	3.4 (2.1)	5.3 (2.1)	0 (0.0)	11.5 (.000)	13,2,4	
Most drinks/occasion, mean (SD)	11.6 (7.1)	14.1(8.9)	12.6 (7.8)	0 (0.0)	35.9 (.000)	1,234	
Drank all 3 trimesters, n (valid%)	9 (81.8)	8 (66.7)	4 (36.4)	0 (0.0)			21.9 (.000)

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FASD 4-Digit Code [K] (n)	1434 (1) 1444 (3) 2444 (2) 3343 (1) 3344 (2) 3444 (1) 4444 (1)	1134 (3) 1234 (5) 1244 (1) 2233 (1) 2244 (1) 4244 (1)	1123 (1) 1124 (2) 1224 (4) 2224 (3) 4223 (1)	1111 (5) 1121 (5) 1211 (1) 1221 (4) 2221 (1)			
Other Prenatal Risk Factors							
Prenatal Rank, 4-Digit Code, n (%)							
1. No risk	0 (0.0)	0 (0.0)	0 (0.0)	16 (100)			
2. Unknown risk	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
3. Some risk	11 (100)	12 (100)	11 (100)	0 (0.0)			
4. High risk	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
Cigarette smoking, n (%)	10 (90.9)	9 (75.0)	8 (72.7)	0 (0.0)			28.5 (.000)
Any illicit drug use, n (%)	6 (54.5)	7 (58.3)	6 (54.5)	0 (0.0)			14.5 (002)
Marijuana use, n (%)	5 (45.5)	4 (33.3)	4 (36.4)	0 (0.0)			8.7 (.03)
Cocaine use, n (%)	3 (27.3)	4 (33.3)	2 (18.2)	0 (0.0)			4.6 (.03)
Poor or no prenatal care, n (%)	4 (36.4)	7 (63.6)	6 (54.5)	0 (0.0)			14.1 (.003)
Gestational age in weeks, mean (SD)	38.7 (1.9)	37.9 (1.3)	39.9 (1.9)	39.3 (1.7)			2.3 (.09)
Other Postnatal Risk Factors							
Postnatal Rank, 4-Digit Code, n (%)							
1. No risk	0 (0.0)	0 (0.0)	0 (0.0)	15 (94.0)			
2. Unknown risk	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
3. Some risk	4 (36.)	7 (58.3)	5 (45.5)	1 (6.0)			
4. High risk	7 (63.6)	5 (41.7)	6 (54.5)	0 (0.0)			
Not living with birth parent, n (%)	8 (72.7)	9 (75.0)	8 (72.7)	1 (6.2)			19.7 (.000)
Number home placements, mean (range)	5.1 (1-27)	3.5 (1-6)	4.3 (1-9)	1.1 (1-2)	2.9 (.04)	123,4	
Age (years) at 1st foster placement mean (SD)	4.7 (4.4)	3.6 (2.8)	3.1 (2.3)	3 (0.0)	.04 (.74)		
Annual household income less than $50,000, n (%)	6 (54.5)	6 (50.0)	2 (18.2)	1 (6.3)			10.4 (.02)
Caregiver education (years), mean (range)	12.4 (11-18)	12.8 (7-18)	14.4 (12-18)	16.3 (7-18)	7.1 (.001)	123,34	
Caregiver occup.: executive level [L] n (%)	1 (9.0)	1 (8.3)	6 (54.5)	8 (50.0)			10.7 (.01)
Physical abuse, n (%)	5 (45.5)	2 (16.7)	3 (27.3)	0 (0.0)			16.2 (.01)
Sexual abuse, n (%)	4 (36.4)	3 (25.0)	5 (45.5)	0 (0.0)			17.7 (.007)

Notations: **A**. Four of the 11 subjects in the FAS/PFAS group had full FAS using the 4-Digit Code. **B**. One subject with PFAS had agenesis of the corpus callosum. **C.** Between groups degrees of freedom = 3; within groups df = total sample size minus 4. **D**. Caucasian versus not Caucasian. **E**. No growth deficiency versus mild to severe growth deficiency. **F**. Definition of Rank 4 FAS Face: palpebral fissure lengths 2 or more SDs below the mean, and lip and philtrum are Rank 4 or 5 on University of Washington Lip-Philtrum Guide. **G**. No child had hypo-or hypertelorism that could impact the validity of the D-score. **H**. Both children with moderate functional impairment had structural evidence of brain abnormality (microcephaly). **I.** Chi-square for FAS/PFAS versus SE/AE. **J**. Chi-square for FAS/PFAS versus SE/AE. **K.** The 4 digits represent the rank for growth, face, brain and alcohol, in that order. **L** Reflects Level 9 Hollingshead occupation: higher executive/proprietor of large businesses.

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Abbreviations: Chi2: chi-square test across the four study groups, unless otherwise specified. Duncan: The Duncan multiple comparison range test is reported if the overall ANOVA is statistically significant; commas separate groups with homogeneous means at $p < 0.05$. F: F statistic. FAS/PFAS: FAS/partial FAS. L: left. ND/AE: Neurodevelopmental Disorder/Alcohol Exposed; Occup. Occupation; OFC: occipital frontal circumference. Overall: Overall assessment of between-group means using ANOVA. p: p-value. R: right. SD: standard deviation. SE/AE: Static Encephalopathy/Alcohol Exposed. Unk: unknown. Z-score: number of standard deviations above/below the population-based mean. $: United States dollars.

Prevalence of risk factors

Among the subjects with FASD, all had confirmed PAE (88% with high Rank 4 alcohol exposures) (Table 2). Seventy-nine percent had prenatal tobacco exposure and 56% had prenatal exposure to illicit drugs (marijuana 38%, cocaine, 27%, heroine 6%, quaaludes 3%, methamphetamines 3%). Seventy-four percent were not living with their birth parents and had on average 4.3 out-of-home placements with the first placement starting at 3.8 years of age on average. Twenty-nine percent were physically abused; 35% were sexually abused. Household annual income was less than $50,000 US dollars in 2009 for 42%. Forty-six percent of their primary caregivers had a high-school degree or less. Although the presence of other risk factors was not restricted for enrollment of controls, the prevalence of other prenatal and postnatal risk factors was significantly lower among the Controls (no prenatal exposure to tobacco or illicit drugs, only one subject (6%) had one out-of-home placement, 19% had a primary caregiver with a high-school degree or less, 6% had an annual household income less than $50, 000, and no reported physical or sexual abuse)..

Prenatal alcohol exposure explained the highest proportion of variance in brain structure and function. Other risk factors explained a significant, but smaller proportion of variance

Prenatal alcohol exposure accounted for up to 34% of the variance (adjusted R^2) in regional brain volumes, up to 52% of the variance in CNS function and up to 51% of the variance in mental health symptoms (Figure 2). Of the various measures of quantity, frequency and timing of PAE available for entry into the regressions, "days per week of drinking during pregnancy" and "drank all three trimesters" demonstrated the strongest, significant correlations with brain outcomes. Other prenatal and postnatal risk factors that met criteria for entry into the regression equations each explained an additional 5-15% of the variance (Figure 2). All correlations between risk factors and brain outcomes were in the direction anticipated (the more severe the risk factor, the more severe the brain outcome). When patient gender entered the equation, being male was associated with more severe functional outcomes and larger brain volumes relative to females.

The order of entry of each risk factor into the regression equation (depicted by the numbers 1, 2, 3 or 4 in the boxes in Figure 2) documents which risk factors explained the greatest proportion of variance in the brain structural, functional or mental health outcomes. For example: of all 14 prenatal and postnatal risk factors available for entry into the regression equation (Figure 2), the number of days/ week of drinking during pregnancy explained the greatest proportion of variation (46%) in the WISC-III Full Scale Intelligence Quotient (FSIQ) [33] score and thus was the first statistically significant risk factor ($p<.05$) to enter into the regression equation. Caregiver's years of education explained the 2nd greatest and statistically significant proportion of variance of the FSIQ (an additional 8% of variance). These two risk factors together explained 54% of the variance in the FSIQ. Maternal drinking through all three trimesters was the third and final statistically significant risk factor to enter the equation, explaining an additional 4% of variance. The three risk factors together explained a total of 58% of the variance in the FSIQ. The regression equation produced was WISC-III FSIQ standard score = 86.9 -2.75 (average number of days/week drinking during pregnancy) +1.7 (Hollingshead's Score for caregiver's years of education (3 through 21 with <7th grade = 3 and post graduate = 21) – 12.4 (drank all 3 trimesters (yes = 1, no = 0)). Higher levels of prenatal alcohol use were correlated with lower FSIQ scores. Higher parental education levels were correlated with higher FSIQ scores.

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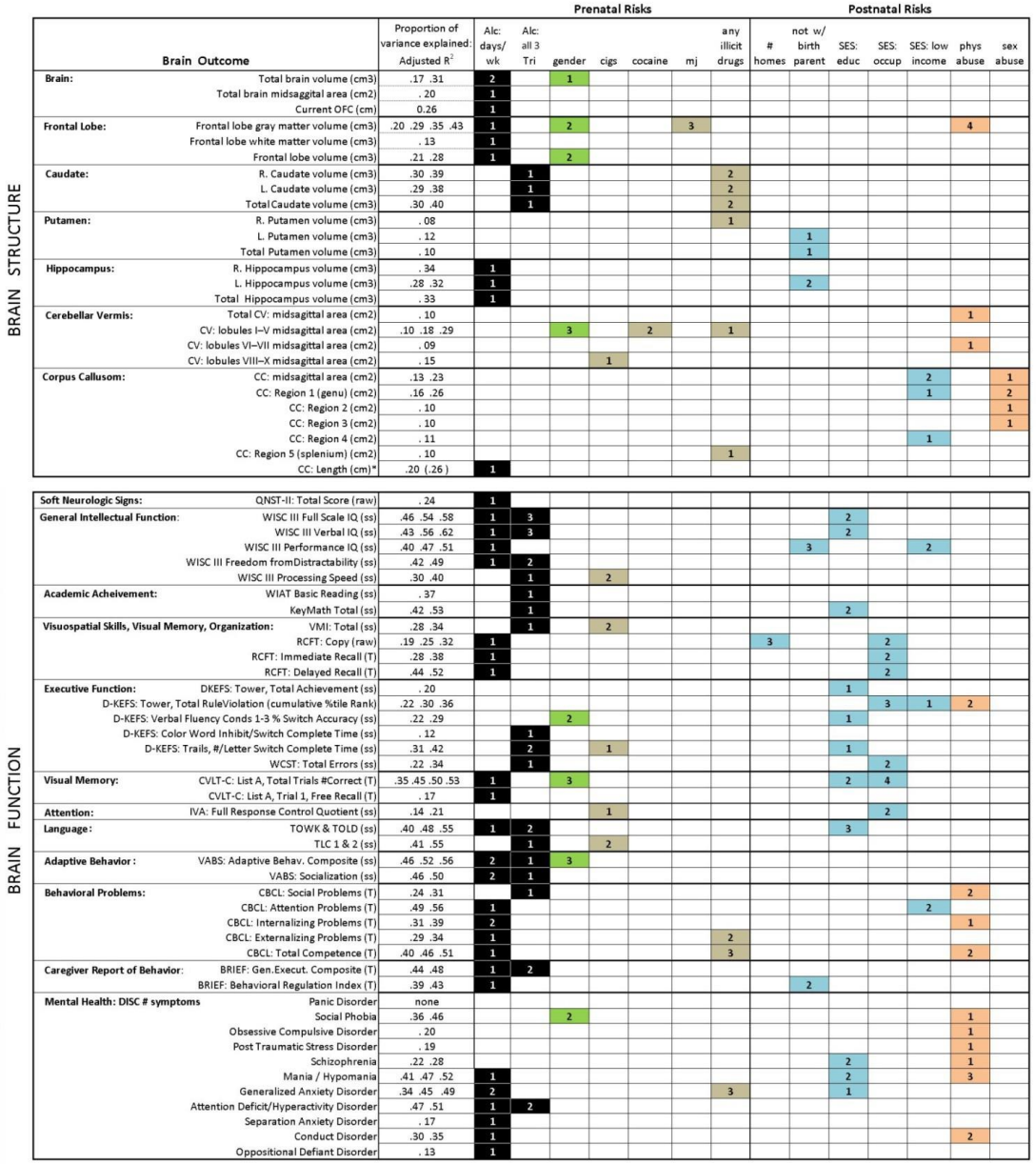

	Brain Outcome		Proportion of variance explained: Adjusted R^2	Alc: days/ wk	Alc: all 3 Tri	gender	cigs	cocaine	mj	any illicit drugs	# homes	not w/ birth parent	SES: educ	SES: occup	SES: low income	phys abuse	sex abuse
				Prenatal Risks							Postnatal Risks						
BRAIN STRUCTURE	**Brain:**	Total brain volume (cm3)	.17 .31	2		1											
		Total brain midsaggital area (cm2)	. 20	1													
		Current OFC (cm)	0.26	1													
	Frontal Lobe:	Frontal lobe gray matter volume (cm3)	.20 .29 .35 .43	1		2			3							4	
		Frontal lobe white matter volume (cm3)	. 13	1													
		Frontal lobe volume (cm3)	.21 .28	1		2											
	Caudate:	R. Caudate volume (cm3)	.30 .39		1					2							
		L. Caudate volume (cm3)	.29 .38		1					2							
		Total Caudate volume (cm3)	.30 .40		1					2							
	Putamen:	R. Putamen volume (cm3)	. 08							1							
		L. Putamen volume (cm3)	. 12									1					
		Total Putamen volume (cm3)	. 10									1					
	Hippocampus:	R. Hippocampus volume (cm3)	. 34	1													
		L. Hippocampus volume (cm3)	.28 .32	1								2					
		Total Hippocampus volume (cm3)	. 33	1													
	Cerebellar Vermis:	Total CV: midsagittal area (cm2)	. 10													1	
		CV: lobules I–V midsagittal area (cm2)	.10 .18 .29			3		2		1							
		CV: lobules VI–VII midsagittal area (cm2)	. 09													1	
		CV: lobules VIII–X midsagittal area (cm2)	. 15				1										
	Corpus Callusom:	CC: midsagittal area (cm2)	.13 .23												2		1
		CC: Region 1 (genu) (cm2)	.16 .26												1		2
		CC: Region 2 (cm2)	. 10														1
		CC: Region 3 (cm2)	. 10														1
		CC: Region 4 (cm2)	. 11												1		
		CC: Region 5 (splenium) (cm2)	. 10							1							
		CC: Length (cm)*	.20 (.26)	1													
BRAIN FUNCTION	**Soft Neurologic Signs:**	QNST-II: Total Score (raw)	. 24	1													
	General Intellectual Function:	WISC III Full Scale IQ (ss)	.46 .54 .58	1	3								2				
		WISC III Verbal IQ (ss)	.43 .56 .62	1	3								2				
		WISC III Performance IQ (ss)	.40 .47 .51	1								3			2		
		WISC III Freedom fromDistractability (ss)	.42 .49	1	2												
		WISC III Processing Speed (ss)	.30 .40		1		2										
	Academic Acheivement:	WIAT Basic Reading (ss)	. 37		1												
		KeyMath Total (ss)	.42 .53		1								2				
	Visuospatial Skills, Visual Memory, Organization:	VMI: Total (ss)	.28 .34		1		2										
		RCFT: Copy (raw)	.19 .25 .32	1							3			2			
		RCFT: Immediate Recall (T)	.28 .38	1										2			
		RCFT: Delayed Recall (T)	.44 .52	1										2			
	Executive Function:	DKEFS: Tower, Total Achievement (ss)	. 20										1				
		D-KEFS: Tower, Total RuleViolation (cumulative %tile Rank)	.22 .30 .36											3	1	2	
		D-KEFS: Verbal Fluency Conds 1-3 % Switch Accuracy (ss)	.22 .29			2							1				
		D-KEFS: Color Word Inhibit/Switch Complete Time (ss)	. 12		1												
		D-KEFS: Trails, #/Letter Switch Complete Time (ss)	.31 .42		2		1						1				
		WCST: Total Errors (ss)	.22 .34		1									2			
	Visual Memory:	CVLT-C: List A, Total Trials #Correct (T)	.35 .45 .50 .53	1		3							2	4			
		CVLT-C: List A, Trial 1, Free Recall (T)	. 17	1													
	Attention:	IVA: Full Response Control Quotient (ss)	.14 .21				1							2			
	Language:	TOWK & TOLD (ss)	.40 .48 .55	1	2								3				
		TLC 1 & 2 (ss)	.41 .55		1		2										
	Adaptive Behavior:	VABS: Adaptive Behav. Composite (ss)	.46 .52 .56	2	1	3											
		VABS: Socialization (ss)	.46 .50	2	1												
	Behavioral Problems:	CBCL: Social Problems (T)	.24 .31		1											2	
		CBCL: Attention Problems (T)	.49 .56	1											2		
		CBCL: Internalizing Problems (T)	.31 .39	2												1	
		CBCL: Externalizing Problems (T)	.29 .34	1						2							
		CBCL: Total Competence (T)	.40 .46 .51	1						3						2	
	Caregiver Report of Behavior:	BRIEF: Gen.Execut. Composite (T)	.44 .48	1	2												
		BRIEF: Behavioral Regulation Index (T)	.39 .43	1								2					
	Mental Health: DISC # symptoms	Panic Disorder	none														
		Social Phobia	.36 .46			2										1	
		Obsessive Compulsive Disorder	. 20													1	
		Post Traumatic Stress Disorder	. 19													1	
		Schizophrenia	.22 .28										2			1	
		Mania / Hypomania	.41 .47 .52	1									2			3	
		Generalized Anxiety Disorder	.34 .45 .49	2						3			1				
		Attention Deficit/Hyperactivity Disorder	.47 .51	1	2												
		Separation Anxiety Disorder	. 17	1													
		Conduct Disorder	.30 .35	1												2	
		Oppositional Defiant Disorder	. 13	1													

Figure 2. Proportion of variance in brain structure and function explained by prenatal and postnatal risks. The order of entry of each risk into the regression equation (depicted by the numbers 1,2,3 or 4 in the colored boxes) documents which risks explained the greatest proportion of variance in the brain structural, functional or mental health outcomes. For example: of 14 prenatal and postnatal risks available for entry into the regression equation, the number of days/week of drinking during pregnancy explained the greatest proportion of variation (46%) in the WISC-III FSIQ score and thus was the first significant risk factor ($p < .05$) to enter into the regression equation. Caregiver's years of education explained the 2nd greatest and statistically significant proportion of variance of the FSIQ (8% additional variance). These two risks together explained 54% of the variance in FSIQ. Maternal drinking all three trimesters was the third and final statistically significant risk to enter the equation, explaining an additional 4% of variance. The three risk factors together explained 58% of the variance in the FSIQ. To further aid interpretation, prenatal and postnatal risks were collapsed into 5 categories depicted by colored boxes: (PAE black; gender green, other prenatal exposures brown, postnatal home environment and caregiver SES blue, and trauma orange). Using this color scheme, one can quickly see how often a particular category of risk explained a significant proportion of variation in brain outcomes. *One subject with PFAS and agenesis of the corpus callosum was removed from the analysis in parentheses. **Abbreviations**: cm centimeters; edu education; L left; mj marijuana; occup occupation; OFC occipital frontal circumference; R right; SES socioeconomic status; ss standard or scaled score; T t-score; Tri trimesters; wk week; # homes number of home placements. See Table 1 for test names.

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To aid in the interpretation of Figure 2, the 14 prenatal and postnatal risk factors were collapsed into 5 categories of risk depicted by the following color scheme: prenatal alcohol is depicted with black boxes; gender with green boxes, other prenatal exposures with brown boxes, postnatal home environment and caregiver SES with blue boxes, and postnatal trauma with orange boxes. Using this color scheme, one can quickly see how often a particular category of risk explained a significant proportion of variation in brain outcomes. Prenatal alcohol exposure explained the greatest proportion of variance (was the first risk factor to be entered into the regression equation) 31% of the time across all brain outcome measures. In other words, 43 of the 138 cells under the two alcohol measures in Figure 2 are black boxes with a number 1 inside the box (43/138 = 31%). In contrast, the remaining risk factor categories (depicted by green, brown, blue and orange boxes) were first to enter the equation as follows: gender 1.4% of the time; other prenatal exposures risks 2.2%; postnatal home environment and SES risks 2.6% and postnatal trauma 7.2%. Prenatal alcohol exposure was also the most common risk factor to enter into a regression equation, irrespective of the order of entry into the equation. In other words, a measure of PAE entered into a regression equation 40% of the time (55 of the 138 cells for PAE in Figure 2 have black boxes). In contrast, the remaining risk factor categories (depicted by green, brown, blue and orange boxes) entered into the equations as follows: gender 11.6% of the time; other prenatal exposures risks 6.2%; postnatal home environment and SES risks 8.7% and postnatal trauma 12.3%.

Discussion

Individuals with PAE often present with a multitude of other prenatal and postnatal risk factors. Based on the outcomes of this study:

1. PAE was the dominant risk factor explaining the largest proportion of variance across the greatest number of brain structural and functional measures. PAE was not the only risk factor influencing brain outcomes.

2. Other prenatal and postnatal risk factors were prevalent and contributed significantly to the adverse brain outcomes. Individually, each risk factor explained a statistically significant, but smaller proportion of variance in brain outcome compared to PAE. In combination, however, the proportion of variance explained by the presence of multiple prenatal and postnatal risks rivaled that of PAE.

These findings pose important implications for prevention and intervention. The proportion of variance explained by each risk factor can help guide which risk factors (when prevented) will have the greatest positive impact on outcome. Clearly, the greatest positive impact on brain outcome is achieved through prevention of both prenatal and postnatal risk factors. But when prevention of prenatal risks does not occur, Figure 2 illustrate the clear benefits of an early FASD diagnosis; maximizing the opportunity to mitigate postnatal risks. The outcomes of this study also illustrate the importance of documenting and addressing the multitude of other prenatal and postnatal risk when diagnosing FASD. The prenatal and postnatal risk factors used to conduct this study were collected during the child's FASD diagnostic evaluation using the FASD 4-Digit Code. These risk factors are formally documented in the electronic 4-Digit Code FASD Diagnostic Form [17] and ranked on 4-point Likert scales (Prenatal Rank and Postnatal Rank) just like the growth, face, brain and alcohol components of the FASD 4-Digit Code.

The prevalence of PAE and other prenatal and postnatal risk factors in a FASD diagnostic clinical population is substantially greater than in the general population. The reported prevalence of these risk factors in the general U.S. population, current study population, and the entire clinical population of 2,461 individuals with PAE evaluated at the University of Washington FASDPN clinic to date, respectively, are as follows: PAE (15%, 100%, 100%), PAE all three trimesters (8%, 62%, 48%); prenatal tobacco exposure (25%, 79%, 71%); marijuana exposure (7%, 38, 36%); cocaine exposure (0.3%, 26%, 34%); any illicit drug exposure (6%, 56%, 42%); foster placement (0.6%, 74%, 64%); physical abuse (8%, 32%, 31%) sexual abuse (10%, 35%, 31%) [34-38].

The patterns of risk that significantly influenced brain structure and function observed in the current exploratory study (Figure 2) present with interesting corollaries in the FASD, trauma, illicit drug exposure and SES literature. These corroborative findings represent an important incremental step toward supporting/validating the outcomes observed in this study. Of particular note was an unexpected inverse correlation observed in the current study between corpus callosum size and

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sexual abuse (Figure 2). Interestingly, this finding is well documented in the trauma literature. Both Rinne-Albers et al., [5] and Teicher et al., [39] found that sexual abuse was the strongest factor influencing reduced corpus callosum size; a correlation observed only among girls. Upon further evaluation of our data, we too found the inverse correlation between corpus callosum size and sexual abuse was only among females (Figure 3). It is theorized that early traumatization is likely to have a major influence on the corpus callosum, as the process of myelinization and selective pruning are typically influenced by stress hormones [6,39,40]. The prevalence of sexual abuse in the current FASD study population is 4-fold higher (35%) than in the general population (10%) [41].

Tobacco is the most commonly used substance during pregnancy-in 2004, up to 25% of U.S. women smoked cigarettes during pregnancy [38]. Carbon monoxide and nicotine from tobacco smoke may interfere with the oxygen supply to the fetus. Nicotine also readily crosses the placenta, and concentrations in the blood of the fetus can be as much as 15% higher than in the mother [3].

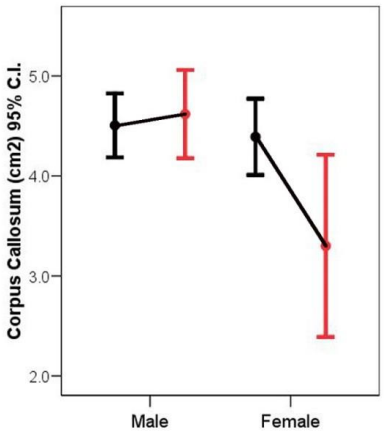

Figure 3. Sexual abuse was the strongest factor influencing reduced corpus callosum size (midsagittal area). As documented in the literature (Rinne-Albers et al., [5], the association in the current study was observed only among females. The mean midsagittal area of the corpus callosum was significantly smaller (3.3, 1.2 SD) among females that experienced sexual abuse compared to females (4.4, 0.9 SD) that did not experience sexual abuse (T = 2.5; p = .03). Key: Error bars reflect the mean and 95% confidence interval. Black: no sexual abuse; Red: sexual abuse

Maternal smoking during pregnancy has been associated with numerous adverse outcomes among offspring including reduced birth weight, inattention, hyperactivity and impulse and emotion control [42,43]. Ekblad, et al., [44] report prenatal smoking exposure was associated with significantly smaller frontal lobe and cerebellar volumes in brains of preterm infants. ADHD has been shown to be related to decreased brain volumes, especially cerebellar volume [45,46]. Consistent with these findings, maternal smoking during pregnancy in the current study was significantly correlated with inattention, reduced cerebellar volume and low birth weight among the offspring. Prenatal tobacco was the strongest significant factor influencing visual and auditory attention and the midsagittal size of cerebellar vermal lobules VIII-X (Figure 2). And although birth weight was not a focus of the current study, we recently found that tobacco exposure (not PAE) was the single strongest factor influencing birth weight centile in a large sample of individuals with FASD (n = 1,814) from our clinical dataset [2]. When we repeated the analysis in the current dataset (using the same array of prenatal and postnatal risk factors and regression model parameters used for the current study),tobacco exposure, once again was the single strongest factor influencing birth weight centile (adjusted R^2 = .17, F 10.2, p =.003). Maternal smoking during pregnancy was 7-fold more prevalent (79%) among the current FASD study population than in the general population of pregnant women (7%).

Child physical abuse is the second most common form of child maltreatment (second to neglect), being reported by 8% of the U.S. adult population [47]. The deleterious effects of child physical abuse on later mental health have been extensively recognized. A history of child physical abuse has been associated with an increased risk of emotional and behavioral problems [7,48], and several psychiatric disorders, including major depression, posttraumatic stress disorder (PTSD), conduct disorder, oppositional defiant disorder, agoraphobia, and generalized anxiety disorder [7,49]. Physical abuse was 4-fold more prevalent (32%) among the current FASD study population than in the general population (8%). In the current study, physical abuse was often the primary factor explaining behavioral problems and six of the eleven childhood psychiatric disorders.

According to a national survey conducted in the United States in 2012 [50], 5.8% of pregnant women used illicit drugs. Marijuana is generally the most commonly used drug during pregnancy, followed by cocaine and opiates. Associations have been found between marijuana use during pregnancy and developmental and hyperactivity disorders among

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children [51-54] and evidence of low birth weight [55]. Prenatal cocaine exposure is related to subtle cognitive, behavioral and physiological differences, including working memory, attention, low birth weight, reduced brain volumes [4] and reduced caudate volumes [56]. In our current study, illicit drug exposure was significantly correlated with behavioral problems and reduced size of several brain regions, most notably the caudate. Of the illicit drugs reported in the current study, marijuana was most common, followed by cocaine. There was no reported prenatal exposure to opiates in this study population born between 1988 and 1996. Illicit drug exposure among the children with FASD was 10-fold higher (56%) than in the general population (6%).

Research shows that lower SES is associated with a wide array of adverse structural and functional brain outcomes in children across development [57]. Functional impairments include language, executive function and memory [8]. Structural abnormalities include smaller volumes of gray matter in hypocampi, middle temporal gyri and occipito-temporal gyri as well as lower diffusivity of the corpus callosum [58]. These findings are highly congruent with our observations. We observed associations between lower SES and impaired neuropsychological function across all domains of function (Figure 2). We also observed an association between lower SES and reduced volume of the corpus callosum. In a recent study focused on a group of children with FASD, Uban et al., [16], typically developing youth with no PAE exhibited increased subcortical brain volumes with increased SES, but surprisingly, the relationship was absent in adolescents with PAE (Figure 2) [16]. We replicated their univariate analysis to see if we too failed to observe a univariate correlation between SES and brain region volume between our Controls and subjects with FASD (Figure 4). It is important to note that 86% of our adolescents with FASD had high (Rank 4) PAE and spanned the full spectrum of FASD (FAS/PFAS, SE/AE and ND/AE). The subjects in the Uban et al., study had confirmed moderate to high PAE, but the severity of their cognitive outcomes or FASD diagnoses was not reported. We observed a somewhat weaker positive association between SES and frontal volume among our FASD group relative to our Control group (Figure 4A). But when we subdivided our FASD group into three groups from most severe to least severe (FAS/PFAS, SE/AE and ND/AE) the positive correlation between SES and frontal lobe volume was actually stronger among the FAS/PFAS than among the Controls (Figure 4B). The strength of the correlation decreased as the severity of FASD decreased from FASD/PFAS to SE/AE to ND/AE. When SES was regressed on WISC FSIQ, significant positive correlations were observed for both Control and FASD study groups (Figure 4C). Within the FASD study group, the strength of the correlation decreased once again as the severity of FASD decreased from FASD/PFAS to SE/AE to ND/AE (Figure 4D). These outcomes provide a potential explanation for why the Uban et al., study did not observe an SES-brain region correlation among the adolescents with PAE. The association could have been missed if the FASD study sample included too few individuals with severe FASD outcomes

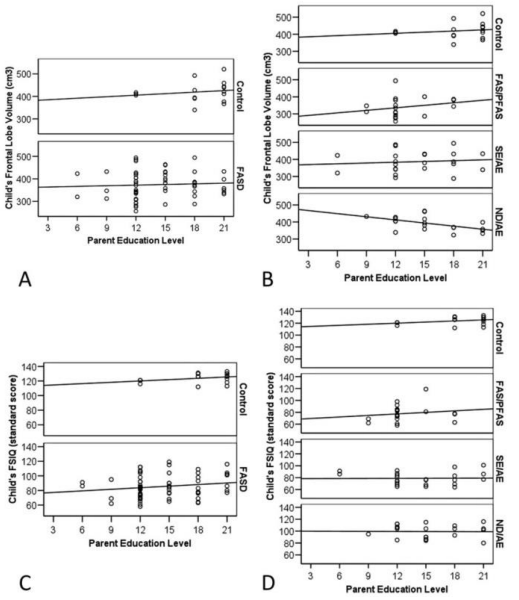

Figure 4. Scatterplots illustrating SES-brain associations for frontal lobe volume and the full scale intelligence quotient. The educational level of the current caregiver is codified in accordance with Hollingshead [24] with 3 reflecting<7th grade education and 21 reflecting a postgraduate education. A) A positive correlation between SES and frontal lobe volume is observed in the Control group, but not the FASD group, consistent with the findings of Uban et al., [16]. B) When the FASD group was subdivided into its three diagnostic categories, it became clear that a strong positive SES-frontal lobe correlation existed in the subgroup with the most severe FASD (the FAS/PFAS subgroup). Weaker correlations were observed among the less severe subgroups (SE/AE and ND/AE groups). The strong positive SES-frontal lobe correlation among children with FAS/PFAS may be masked if combined with children with less severe forms of FASD. C & D) Similar patterns of correlation were observed between SES and Full Scale IQ (FSIQ) with the strongest positive correlations observed among the FAS/PFAS group

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Strengths and limitations

The observations in the current study are based on a small, but rigorous and comprehensive set of data. Replication in other datasets will be important to support/validate the outcomes observed in this exploratory study. To that end, we ran a few internal validation analyses on this current dataset to see if we could replicate findings observed in our larger clinical dataset. For example, as described in the Discussion section, we documented that prenatal tobacco exposure (not PAE) was the single FASD from the University of Washington FASDPN clinic [2]. When we replicated that analysis in the current dataset, once again, prenatal tobacco exposure was the single strongest factor influencing birth weight (adjusted R^2 = 0.17, F 10.2, p =.003). Another correlation that is well documented in our large clinical dataset [23] as well as our large population-based foster care FAS screening dataset [59] is the specificity of the Rank 4 FAS facial phenotype to PAE. When we regressed the same array of prenatal risk factors on a continuous measure of the FAS facial phenotype severity (the FAS facial d-score [27], as hypothesized, only PAE (days/week of drinking during pregnancy) explained a significant proportion of the variance in the FAS facial phenotype (adjusted R^2 = .16, F 10.1, p = .003). Finally, when we conducted a regression analysis in our larger clinical dataset using the same 14 prenatal and postnatal risk factors and regression model parameters to predict FSIQ, maternal drinking through the 3rd trimester explained the largest proportion of variance, with birth mother's years of education entering second and child neglect entering third explaining a total of 23.6% of the variance in FSIQ. This outcome was near identical to the outcome observed in the current study despite the fact that different metrics were used to document the prenatal and postnatal risk factors and the FSIQ was derived from various versions of the WISC (as is typical for a clinical dataset). Although 14 prenatal and postnatal risk factors were assessed in the current study, many other risks exist (e.g. pregnancy complications, prematurity, family genetics, parental verbal abuse, witnessing domestic violence, neglect, etc.). Understanding the interplay between risk factors and outcomes is complex. Teicher and Samson [9] present a series of questions that help convey this complexity and serve as a guide for future studies. 1) Does childhood abuse affect brain structure and function? 2) Does the type of maltreatment matter or are they all stressors? 3) Does age at the time of abuse matter? 4) What is the temporal association between exposure and brain changes? 5) Are boys and girls affected in the same way? 6) Do the observed structural and functional consequences make more sense as adaptive responses or as nonspecific damage? 7) Are the neurobiological consequences of childhood maltreatment reversible? 8) What is the relationship between childhood abuse, brain changes and psychiatric illness?

Conclusion

In conclusion, individuals with PAE present with a multitude of other prenatal and postnatal risk factors. The prevalence of these risk factors is often 3 to 7-fold higher than in the general population. PAE was the dominant risk factor explaining the largest proportion of variance in brain structural and functional outcomes in this study. Individually, each of the other risk factors explained a statistically significant, but smaller proportion of variance in brain outcome compared to PAE. In combination, however, the proportion of variance explained by the presence of multiple prenatal and postnatal risks rivaled that of PAE. A better understanding of the impact other prenatal and postnatal risk factors have on the neurodevelopmental outcomes of individuals with FASD can inform more effective primary prevention and intervention strategies.

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ADVANCES IN PEDIATRIC RESEARCH

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Research Article

High facial specificity and positive predictive value are required to diagnose fetal alcohol syndrome when prenatal alcohol exposure is unknown

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ABSTRACT

Background: Facial criteria with high specificity and positive predictive value (PPV) to prenatal alcohol exposure (PAE) are required to diagnose fetal alcohol syndrome (FAS) when documentation of PAE is unavailable. Not all fetal alcohol spectrum disorder (FASD) diagnostic guidelines appear to meet these criteria.

Methods: A dataset generated from a 10-year FAS screening of 1,602 children in fostercare conducted by the University of Washington FAS Diagnostic & Prevention Network was used to determine how well the FAS facial phenotype, microcephaly and growth deficiency (individually and in combination at varying levels of magnitude) predicted PAE.

Results: The 4-Digit-Code Rank 4 FAS facial phenotype was the only outcome that provided sufficient PPV and specificity to PAE (100%) to allow the facial phenotype to serve as confirmation of PAE in a diagnostic setting when PAE is unknown. Even minimal relaxation of the phenotype (e.g., Face Rank 3) resulted in PPV (35%) and specificity (88.7%) values too low to use as confirmation of PAE. Further relaxation of the facial criteria, as defined by the Hoyme et al., FASD guidelines, resulted in even lower PPV (17.9%) and specificity (76.6%); both too low to serve as confirmation of PAE in a diagnostic setting. The presence of all three physical features of FAS (Hoyme et al. FAS facial phenotype, growth and OFC ≤10th percentile) did not increase PPV beyond chance (52%).

Conclusion: FASD diagnostic guidelines that use relaxed criteria for the FAS facial phenotype risk misdiagnosing and over-diagnosing FAS and partial FAS when PAE is unknown.

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Introduction

Fetal alcohol syndrome (FAS) is a permanent birth defect syndrome caused by prenatal alcohol exposure (PAE). FAS is characterized by growth deficiency, a unique facial phenotype and structural and/or functional brain abnormalities [1,2]. To date, all fetal alcohol spectrum disorder (FASD) diagnostic guidelines permit a diagnosis of FAS and/or partial FAS (pFAS) to be rendered when a history of prenatal alcohol exposure is unknown [2-7]. Why? For most guidelines, it is because the diagnostic criteria for FAS require the presence of the FAS facial phenotype and the "FAS" facial phenotype is so unique to (caused only by) PAE, its presence serves as confirmation of PAE when written or verbal documentation of PAE is unavailable [2,8-10].

There are four screening metrics used in medicine to quantify how well the presence of a feature (e.g., the FAS facial phenotype) predicts the presence/absence of an exposure (e.g. PAE), and how well an exposure (e.g. PAE) predicts the presence/absence of an outcome (e.g., the FAS facial phenotype). These four metrics (positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity) are defined in Figure 1 [11,12].

If PAE is the only cause of the FAS facial phenotype [8,9,13], one would expect these two conditions to be true:

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		True Exposure		
		Prenatal Alcohol Exposure Documented	Prenatal Alcohol Exposure Not Documented	
Predicted Exposure based on the face	FAS Face Present (Face Rank 4)	True Positive (TP) = **20**	False Positive (FP) = **0**	**Positive Predictive Value (PPV) = 100%** = TP/ (TP + FP) = 20 / (20 + 0)
	FAS Face Absent (Face Ranks 1,2,3)	False Negative (FN) = **207**	True Negative (TN) = **1375**	**Negative Predictive Value (NPV) = 87.0%** = TN/ (FN + TN) = 1375 / (207 + 1375)
		Sensitivity 8.8% = TP / (TP + FN) = 20 / (20 + 207)	**Specificity 100.0%** = TN / (FP + TN) = 1375 / (0 + 1375)	

Figure 1. Demonstration: The ability of the Rank 4 FAS facial phenotype to correctly predict prenatal alcohol exposure.
Among 1,602 children in foster care, 14.2% had documented prenatal alcohol exposure (PAE). If the 4-Digit Code Rank 4 FAS facial phenotype is to be used to confirm PAE when a written or verbal history of exposure is not available, then the FAS facial phenotype must have a high PPV (all individuals with the facial phenotype have a documented PAE) and high specificity (the Rank 4 FAS face is never present in an individual with confirmed absence of PAE).
PPV: Probability that a subject with the FAS facial phenotype has PAE.
NPV: Probability that a subject without the FAS facial phenotype does not have PAE.
Sensitivity: Probability that a subject with PAE has the FAS facial phenotype.
Specificity: Probability that a subject without PAE does not have the FAS facial phenotype.

1. All individuals with the FAS facial phenotype will have PAE (PPV = 100%).
2. No individual with a confirmed absence of PAE will have the FAS facial phenotype (specificity = 100%).

And if, as research supports [14-17], the FAS facial phenotype is caused by prenatal alcohol exposure during a very narrow window of time (~weeks 2 and 3 of pregnancy, gastrulation stage of fetal development), one would expect these two conditions to be true:

1. Absence of the FAS facial phenotype would not confirm absence of PAE (NPV will be low).
2. Not all individuals with PAE would have the FAS facial phenotype (sensitivity will be very low).

While all FASD diagnostic systems allow a diagnosis of FAS to be rendered in the absence of a confirmed PAE, not all FASD diagnostic systems use the same clinical criteria for the FAS facial phenotype. The Australian 2016 [5] and Canadian 2015 [4] systems use the Rank 4 FAS facial phenotype as defined by the 4-Digit Code [3] (three facial features must be present (palpebral fissure lengths (PFL) at or below the 3rd percentile; a smooth philtrum (Rank 4 or 5 on the University of Washington (UW) Lip-Philtrum Guides) and a thin upper lip (Rank 4 or 5 on the UW Lip-Philtrum Guides)). The CDC 2004 guidelines use the 4-Digit Code criteria with one exception (the PFL criteria is relaxed to ≤10th percentile) [6]. The criteria for the FAS facial phenotype used by the Hoyme et al., 2016 [7] FASD diagnostic system is the most relaxed (only 2 of the 3 facial features must be present and 2 of the 3 facial features are relaxed in their magnitude relative to the 4-Digit Code (PFLs ≤ 10th percentile; a smooth philtrum (Rank 4 or 5 on the Hoyme et al., Lip/Philtrum Guides) and/or a thin upper lip (Rank 4 or 5 on the Hoyme et al., Lip/Philtrum Guides)). The Rank 4 thin upper lip on the Hoyme et al., North American Lip/Philtrum Guide is confirmed equivalent to the Rank 2 moderately thick upper lip on the UW Lip-Philtrum Guide [18,19].

When the 4-Digit-Code Rank 4 FAS facial phenotype was first identified and case-defined in a small, but rigorous split-half empirical study, PPV and specificity to FAS and PAE were 100% [20]. Subsequent studies in large clinical, foster care and general populations continued to document high PPV and specificity to PAE (> 95%) [8,9,13]. The specificity of the more relaxed Hoyme et al., FAS facial phenotype ranges from 71% to 75% as reported by the authors of the guidelines [21] and replicated in the FASDPN datasets [18,19]. A facial specificity of 71% to 75% is not sufficient to allow a valid diagnosis of FAS to be rendered when written or verbal documentation of PAE is unavailable. A specificity of 75% means 25% of individuals who present with the Hoyme et al., FAS facial phenotype do not have PAE. This was illustrated among twelve high functioning children (mean full scale IQ = 120) with confirmed absence of PAE enrolled as controls in a FASD MRI study [22]. Due to the relaxation of the facial criteria, 3 of the twelve children (25%) met the criteria for the Hoyme et al., FAS facial phenotype despite confirmed absence of PAE.

If a FAS facial phenotype with low specificity and PPV is used to confirm PAE, birth mothers are at risk of being wrongly accused of drinking during pregnancy and harming their unborn child; FAS will be misdiagnosed and over-diagnosed, and studies designed to generate population-based estimates of the prevalence of FAS will lead to inaccurate over-estimates [10].

If the criteria used to define the FAS facial phenotype do not have sufficiently high specificity and PPV to confirm PAE, can the specificity and PPV be increased by requiring additional FAS physical features be present? For example, what is the specificity and PPV to PAE when an individual presents with the FAS facial phenotype and microcephaly and growth deficiency? To answer this question, a dataset generated from a 10-yr population-based FAS screening of 1,602 children in foster care was used [9]. The screening activity collected height, weight, head circumference, computerized facial measures from facial photographs and presence/absence of documented PAE for each child.

The primary objective of this study was to determine how well the FAS facial phenotype, microcephaly and growth deficiency (individually and in combination at varying levels of magnitude) predict prenatal alcohol exposure. The following outcomes were postulated:

1. If the FAS facial phenotype is to be used to confirm PAE when a written or verbal history of exposure is not available, then the FAS facial phenotype must have 100% PPV (all people with the facial phenotype have PAE) and 100% specificity (the Rank 4 FAS face is never present in a person with confirmed absence of PAE).
2. Relaxation of the FAS facial phenotype criteria will cause a sharp drop in specificity and PPV to PAE.
3. The majority of individuals with PAE will not present with the FAS facial phenotype because there is a very narrow window of vulnerability in which PAE can cause the FAS facial features during fetal development (gestational weeks 2-3: the gastrulation stage) [16,17]. The sensitivity of the FAS

facial phenotype to predict PAE will be very low. If one were to use the FAS facial phenotype to screen a population for PAE, most of the individuals with PAE would be missed.

4. Since the majority of children in this foster care population are not expected to have the FAS facial phenotype and the majority will not have a documented PAE, the absence of the FAS facial phenotype will correctly predict the absence of PAE in the majority of the children in this foster care population by chance alone. NPV values will be uniformly higher under these circumstances as described more fully below, but this does not mean the absence of the FAS facial phenotype can be used to accurately rule-out PAE. NPV will not be 100%. It is well understood that the majority of individuals with PAE do not present with the FAS facial phenotype due to the narrow window of vulnerability in which PAE can cause the FAS facial phenotype.
5. Growth deficiency and microcephaly are caused by PAE but are not unique to (caused only by) PAE. PPV will be very low.
6. If the criteria for the FAS facial phenotype are relaxed, the combined presence of the relaxed facial phenotype, growth deficiency and microcephaly should increase specificity and PPV to PAE, but may not increase it sufficiently (> 95%) to serve as diagnostic confirmation of PAE when a verbal or written confirmation of PAE is not available.

Research Methodology

The dataset used for this study was generated from a 10-year FAS screening study of 1,602 children in foster care conducted by the University of Washington Fetal Alcohol Syndrome Diagnostic & Prevention Network (FASDPN) and the King County Washington Foster Care Passport Program (FCPP) between 1999 and 2009. Detailed methods and the outcomes of the first 600 children screened were reported in 2004 [9].

Enrollment into the foster care passport program

Briefly, all children, who were legally dependent with the State of Washington and enrolled in the Foster Care Passport Program (FCPP) in King County, Washington between 1999 and 2009 were eligible to participate in the FAS screening [9]. To be enrolled in the FCPP, a child had to be: a) legally supervised by the Department of Social and Family Services; b) 0-12 years of age at the time of enrollment, but may remain in the program after their 12th birthday; c) dependent and d) in out-of-home placement. Upon enrollment in the FCPP, each child's health and social service history from birth to present was abstracted from the child's medical records by a FCPP public health nurse and entered into a foster care Health & Education database. The database was used to produce a summary medical report for each child (a Health and Education "passport") along with health recommendations to be shared with the social worker, the foster parent and the child's health care provider(s). The "passport" included measures of height, weight and head circumference, medical conditions/concerns, and prenatal exposures.

Enrollment into the FAS screening

The FCPP identified all eligible children, obtained written consent from the child's legal guardian (Department of Child and Family Services social worker), sent the child's foster parents a letter that explained the purpose and process of the FAS screening, and sent the FASDPN clinic the list of all newly eligible, consented children, weekly. The FASDPN scheduler called each foster parent to schedule a photography appointment with the FASDPN photographer. The photographer measured the child's head size (occipital frontal circumference) and took 3 digital standardized facial photographs (frontal, oblique, and lateral) with a ¾ inch round paper sticker placed between the child's eyebrows to serve as an internal measure of scale (Figure 2A). The facial photographs were analyzed by the author using the FAS Facial Photographic Analysis Software, masked to the child's PAE status [23]. Over 95% of eligible children participated in the FAS screening program over a 10-year period [9].

Screen-positive criteria

A child screened positive for FAS if they presented with the Rank 4 FAS facial phenotype as defined by the FASD 4-Digit Code. This facial phenotype is defined below and illustrated in Figure 2.

All children who screened positive were eligible to receive a comprehensive diagnostic evaluation and treatment plan at the FASDPN clinic by an interdisciplinary team (pediatrician, psychologist, speech language pathologist, occupational therapist, social worker and family advocate) using the 4-Digit Diagnostic Code. The screening activity was approved by the Human Research Review Boards of Washington State and the University of Washington. The outcomes of the screening program are reported separately [9].

Study dataset

The following fields of data from the 10-year FAS screening study were used in the current study.

- The 3 individual facial features of FAS were measured from digital facial photographs using the FAS Facial Photographic Analysis Software [23] (Figure 2). A brief video demonstration of the software is provided at this weblink: http://depts.washington.edu/fasdpn/movie/software1024-768cd2.mp4

  1. Palpebral fissure lengths in mm.
  2. Philtrum smoothness: 5-point Likert Rank on the UW Lip-Philtrum Guides
  3. Lip thinness (circularity) was measured by outlining the perimeter of the upper lip using the FAS Facial Photographic Analysis Software [23]. Circularity equals perimeter2/area. The thinner the upper lip, the larger the circularity. The circularity tables printed on the backside of each Lip-Philtrum Guide (Figure 2B) were used to convert lip circularity into lip rank.

- Height (cm) and weight (kg) at enrollment into the screening study and at earlier time points when available in the medical records. The WHO [24] and CDC [25] growth charts were used to generate height and weight percentiles adjusted for age and gender. The FASD 4-Digit Code ranks growth deficiency on a 4-point Likert scale (Rank 1 normal; Rank 2, mild; Rank 3 moderate and Rank 4 severe) in

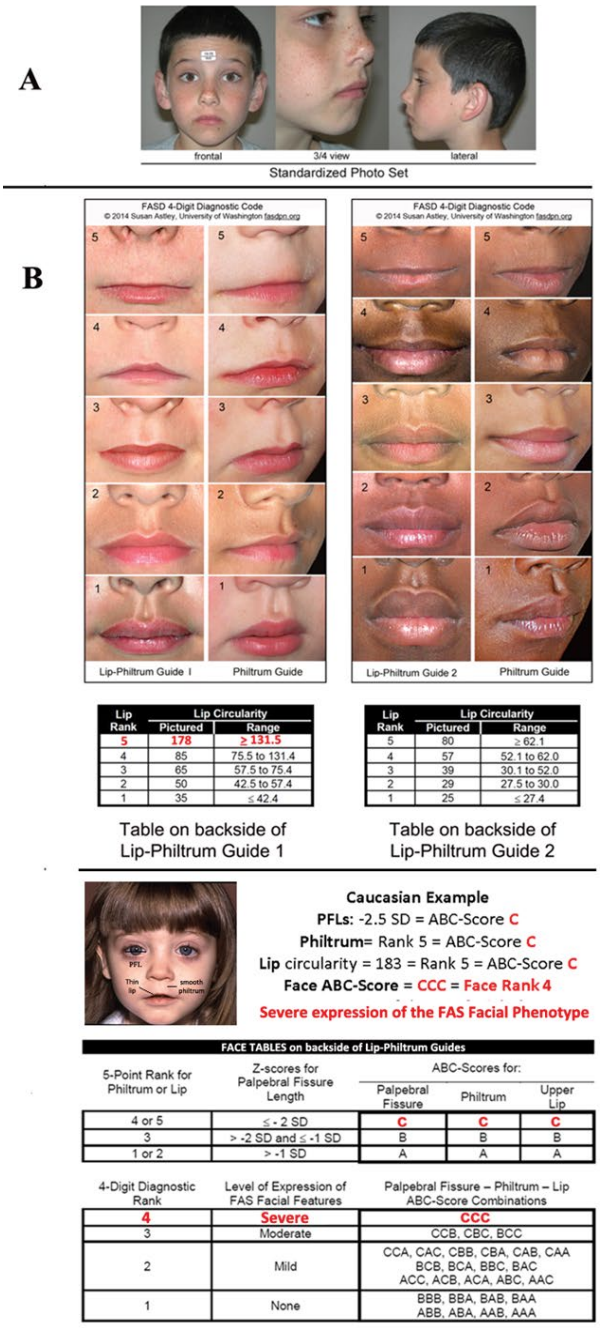

Figure 2. The FASD 4-Digit Code method for measuring the FAS facial phenotype using the FAS Facial Photographic Analysis Software [3,10,23]. The Rank 4 FAS facial phenotype is defined by 3 features: short PFLs ≤ -2 SDs, smooth philtrum Rank 4 or 5 and thin upper lip Rank 4 or 5 on the University of Washington Lip-Philtrum Guides. A) Three digital facial photographs are obtained with a ¾ inch adhesive sticker serving as an internal measure of scale. B) The PFL is measured in mm by clicking the mouse on the inner and outer corners of each eye. Using the Face Tables, the software converts the PFL in mm to a z-score and then to a PFL ABC-Score. The red perimeter of the upper lip is traced with the mouse to compute lip circularity (perimeter^2/area). The software converts lip circularity to lip rank and then to a lip ABC-Score. Finally, the software converts the philtrum rank to a philtrum ABC-Score. The 3 individual ABC-scores are combined in the order PFL-Philtrum-Lip to create the overall Facial ABC-Score. Highlighted in red font is an example of a child with PFL -2.5 SDs, philtrum Rank 5 and lip circularity 183. These three features produce a facial ABC-Score of CCC, representing the severe expression of the FAS facial phenotype (Face Rank 4). The FAS facial phenotype presents on a continuum: Rank 1: none of the 3 features present; Rank 2: 1 or 2 features present; Rank 3: 2.5 of the 3 features present; and Rank 4: all 3 features present. A video demonstration of the facial software is presented at this weblink: https://depts.washington.edu/fasdpn/movie/software1024-768cd2.mp4 Copyright Susan Astley Hemingway University of Washington

accordance with the Growth Tables printed on the backside of the Lip-Philtrum Guides (Figure 3). The Hoyme et al., FASD guidelines dichotomize growth deficiency as present (height and/or weight ≤ 10th percentile) or absent.

- Occipital frontal circumference (OFC) in cm at the time of enrollment in the screening and earlier time points when available in the medical records. The WHO [24] and CDC [25] growth charts were used to generate OFC percentiles adjusted for age and gender. The 4-Digit Code defines microcephaly as OFC ≤ 3rd percentile. The Hoyme et al., FASD guidelines define "microcephaly" as OFC ≤ 10th percentile.
- PAE (documented, not documented) from review of all medical and social service records from birth to present.
- Gender
- Age in years at screening
- Race/ethnicity

The 3 FAS facial features (PFL in mm, philtrum rank, and lip circularity) were used to generate the following FAS facial phenotypes in accordance with the 4-Digit Code [2,3] and Hoyme et al., 2016 [7] FASD diagnostic systems:

4-Digit Code FAS facial phenotype:

The magnitude of expression of the FAS facial phenotype is ranked on a 4-point Likert scale in accordance with the lip circularity and face tables printed on the backside of each Lip-Philtrum Guide (Figure 2B). The FAS facial phenotype (Face Rank 4) requires the presence of all three facial features: 1) palpebral fissure lengths ≤ 3rd percentile, 2) a smooth philtrum (Likert rank 4 or 5 on the UW Lip-Philtrum Guide) and 3) a thin upper lip (Likert rank 4 or 5 on the 5-point Lip-Philtrum Guide) (Figure 2B). The Iosub [26] PFL growth charts were used to generate PFL percentiles by gender and age for all full and mixed race African American children. The Stromland Scandinavian [27] PFL growth charts were used for all other races. The UW Lip-Philtrum Guide 1 was used to Rank lip thinness and philtrum smoothness for Caucasians and all races that indigenously present with thinner lips like Caucasians. The UW Lip-Philtrum Guide 2 was used to Rank lip thinness and philtrum smoothness for African Americans and all races (e.g., aboriginal Australians and some east Asian populations) that indigenously present with thicker lips like African Americans. Based on the racial makeup of the current study population, Lip-Philtrum Guide 2 was used on all full and mixed-race African Americans; Lip-Philtrum Guide 1 was used on all other races. The 27 Asian children in this study were not east Asian.

Hoyme et al., 2016 FAS Facial Phenotype:

The Hoyme et al., FAS facial phenotype is classified on a dichotomous scale (present/absent). The Hoyme et al., FAS facial phenotype requires 2 of the following 3 facial features (PFLs ≤ 10th percentile; smooth philtrum (Rank 4 or 5 on the Hoyme et al., Lip/Philtrum Guides); thin upper lip (Rank 4 or 5 on the Hoyme et al., Lip/Philtrum Guides)) [7]. Hoyme et al., provide two Lip/Philtrum Guides; one for South African Cape Coloured [28] and one for North Americans [7]. The Cape Coloured Lip/Philtrum Guide is not appropriate for use on African Americans, for it was

GROWTH TABLES

Percentile Range	ABC-Scores for: Height	Weight
≤ 3rd	C	C
> 3rd and ≤ 10th	B	B
> 10th	A	A

4-Digit Diagnostic Rank	Growth Deficiency Category	Height-Weight ABC-Score Combinations
4	Severe	CC
3	Moderate	CB, BC, CA, AC
2	Mild	BA, BB, AB
1	None	AA

Example
Height: 8th percentile = ABC-Score B
Weight: 2nd percentile = ABC-Score C
Height-Weight ABC-Score = BC = Growth Rank 3
Moderate Growth Deficiency

Figure 3. FASD 4-Digit Code growth tables for converting height and weight percentiles into Growth Ranks.

The FASD 4-Digit Code documents growth deficiency on a 4-point Likert scale from Rank 1 normal growth to Rank 4 severe growth deficiency. Highlighted in red font is an example of an individual who presented with a height at the 8th percentile and weight at the 2nd percentile. Using the Growth Tables printed on the backside of the Lip-Philtrum Guides, these growth percentiles would translate into a Growth Rank 3, moderate growth deficiency.

developed by Hoyme et al. specifically for the Cape Coloured (mixed race) population in the Western Cape Province of South Africa. The investigators reported that neither of the University of Washington Caucasian or African American Lip-Philtrum Guides were an exact "fit" for the Cape Coloured population. Due to the absence of a Hoyme et al. Lip/Philtrum guide appropriate for use on African Americans, the Hoyme et al., FAS facial phenotype was not generated for subjects in this study that were full or mixed race African American. For all other races, the Hoyme et al., North American Lip/Philtrum Guide was used to Rank lip thinness and philtrum smoothness. Based on a previous study [18], the Rank 4 lip on the Hoyme et al., North American Lip/Philtrum Guide has a circularity of 52.5 (see video demonstration at this weblink: http://depts.washington.edu/fasdpn/movie/Fig2Cvideo.mp4). Thus, all lips with circularity ≥ 52.5 met the Hoyme et al., FAS facial phenotype criteria for a "thin upper lip". The Stromland [27] PFL normal growth charts were used to generate PFL percentiles adjusted for gender and age.

Specificity, sensitivity, PPV and NPV were calculated in accordance with Figure 1 to determine how accurately the FAS facial phenotype, microcephaly and growth deficiency (individually and in combination at varying levels of magnitude) predict PAE. Confidence intervals for sensitivity and specificity are "exact" Clopper-Pearson confidence intervals [29]. Confidence intervals for the predictive values are the standard logit confidence intervals given by Mercaldo et al. [30].

Sensitivity: (true positive rate) The proportion of people with documented PAE that have the FAS facial phenotype. We expect sensitivity to be very low; most people with PAE do not present with the FAS facial phenotype. If the FAS facial phenotype was used to screen for individuals with PAE, most individuals with PAE would be missed.

Specificity: (true negative rate) The proportion of people with no documented PAE that do not have the FAS facial phenotype. We expect specificity to be very high. If PAE is the only cause of the FAS facial phenotype, then a person cannot have the FAS facial phenotype if they were not exposed to alcohol.

PPV: The probability that a person with the FAS facial phenotype has a documented PAE. We expect this to be very high. If PAE is the only cause of the FAS facial phenotype, then a person with the FAS facial phenotype must have been exposed to alcohol in-utero.

NPV: The probability that a person without the FAS facial phenotype has no documented PAE. We expect this to be relatively high for the reasons outlined below.

Sensitivity and specificity are attributes of the diagnostic test. They are not influenced by the prevalence of PAE in the population. PPV and NPV are influenced by the sensitivity and specificity of the test and by the prevalence of PAE in the study population. As the prevalence of PAE decreases, the PPV (the ability of the FAS facial phenotype to correctly predict PAE) decreases because there will be more false positives for every true positive. This is because one is hunting for a "needle in a haystack" (e.g. only 14% of the children in this foster care have documented PAE). Since there are so many more children without documented PAE (86%) in this foster population, chance alone dictates one has a greater probability of selecting a child without documented PAE, than one with documented PAE. As the prevalence of PAE decreases, the NPV (the ability of the absence of the facial phenotype to correctly predict the absence of PAE) increases because there will be more true negatives for every false negative. Again, since there are so many more children without documented PAE (86%) in this foster care population, chance alone dictates one has a greater probability of selecting an individual without documented PAE, than one with PAE.

Results

Sociodemographic and FASD clinical profiles

The sociodemographic and FASD clinical profiles of the 1,602 children in foster care that participated in the FAS screening are presented in Table 1. The population was predominantly Caucasian (52%) and full or mixed race African American (31%); ranged in age from 3 months to 17 years old with 47% under 4 years of age. Roughly half (49%) were female.

Growth deficiency (height and/or weight ≤ 10th percentile) was observed in 14% of the population.

The 4-Digit Code Rank 4 FAS facial phenotype was observed in 20 (1.2%) of 1,602 children across all races (13 (2.6%) among the 502 African American; 7 (0.6%) among the remaining 1,100 children from all other races). The prevalence of PAE was highest (18.5%) among the 502 African American; 12.1% among all other races. Of the 20 with the Rank 4 FAS facial phenotype, 100% had documented PAE. The Hoyme et al., FAS facial phenotype was observed in 274 (25%) of the 1,093 children from all races except African Americans (exclusion of African Americans is explained above). Of the 274 with the Hoyme et al., FAS facial phenotype, 17.9% had documented PAE.

OFC ≤ 3rd percentile (microcephaly) was observed among 6.6% of the 1,602 children. OFC ≤ 10th percentile was observed among 11.7% of the children.

Prenatal alcohol exposure was documented in 227 (14.2%) of the 1,602 children.

Specificity, sensitivity, PPV and NPV

The PPV, NPV, specificity and sensitivity documenting how well the FAS facial phenotype, microcephaly and/or growth deficiency (individually and in combination at varying levels of magnitude) predicted prenatal alcohol exposure is presented in Table 2.

Table 1. Sociodemographic and clinical profile of the 1,602 children that participated in the foster care FAS screening.

Characteristic		Total N 1,602	
Race (n, %)	Caucasian	828	51.7
	African American (full or mixed-race)	502	31.3
	Native American	157	9.8
	Hispanic	26	1.6
	Asian	27	1.7
	All others including mixed race	62	3.9
Age years (n, %)	0-3.9	756	47.2
	4-5.9	210	13.1
	6-8.9	235	14.7
	9-12.9	328	20.5
	13-17.4	73	4.6
	mean (SD) range	5.5 (4.2)	0.3-17.4
Gender (n, %)	female	778	48.5
Growth Rank[A] (n, %)	normal (height & weight > 10th percentile): Rank 1	1383	86.3
	mild (height and/or weight 4-9th percentile): Rank 2	146	9.1
	moderate (height or weight ≤ 3rd percentile): Rank 3	32	2
	severe (height & weight ≤ 3rd percentile): Rank 4	41	2.6
	height and/or weight ≤ 10th percentile	219	13.7

FAS face Rank[A] (n, %)	normal (none of the 3 features): Rank 1	776	48.4
	mild (1 or 2 of the 3 features): Rank 2	685	42.8
	moderate (2.5 of the 3 features): Rank 3	121	7.6
	severe (all 3 features): Rank 4	20	1.2
Head Circumference (n, %)	microcephaly: OFC ≤ 3rd percentile	95	6.6
	microcephaly: OFC ≤ 3rd percentile & PAE	35	2.4
	OFC ≤ 10th percentile	167	11.7
	OFC ≤ 10th percentile & PAE	43	3
Prenatal alcohol exposure (n, %)	none documented	1,375	85.8
	documented	227	14.2

A. See Figures 2 and 3 for how growth and face are Ranked by the FASD 4-Digit Code.

Abbreviations: OFC: occipital frontal head circumference; PAE: prenatal alcohol exposure

Specificity and PPV of the FAS facial phenotype

The 4-Digit-Code Rank 4 FAS facial phenotype was 100% specific to PAE and 100% PPV for PAE. Twenty children presented with the Rank 4 FAS facial phenotype; all 20 had documented PAE (100% PPV). Of the 1,330 children with no documented PAE; none presented with the Rank 4 FAS facial phenotype (100% specificity).

Of the 274 children that presented with the Hoyme et al., FAS facial phenotype; only 49 had documented PAE (17.9% PPV). The Hoyme et al., FAS facial phenotype was not predictive of PAE. The vast majority (82.1%) with the Hoyme et al., FAS facial phenotype did not have documented PAE. Of the 960 children with no documented PAE; 735 did not have the FAS facial phenotype (76.6% specificity). In other words, 23.4% of the children with no documented PAE presented with the Hoyme et al., FAS facial phenotype. If the University of Washington Lip-Philtrum Guide 1 for Caucasians was used instead of the Hoyme et al., North American Lip-Philtrum Guide, 121 children presented with the Hoyme et al., FAS facial phenotype. Of these 121 children; only 36 had documented PAE (29.8% PPV). Relaxation of the PFL to the 10th percentile and requiring only two of the three facial features continued to produce a FAS facial phenotype that was not predictive of PAE.

Since the magnitude of expression of the 4-Digit Code FAS facial phenotype is ranked on a 4-point Likert scale from Rank 1 (absent) to Rank 4 (fully present), the specificity, sensitivity, PPV and NPV were calculated for each Rank to assess how incremental relaxation of the FAS facial phenotype impacts the phenotype's ability to predict PAE (PPV). When the mild Rank 2, moderate Rank 3 and severe Rank 4 expressions of the FAS facial phenotype were compared to Rank 1 (complete absence of the FAS facial phenotype), the ability of the FAS facial phenotype to predict PAE (PPV) dropped precipitously from 100% for the Rank 4 face to 26.5% for the Rank 3 face (Table 2). The PPV for the Rank 2 face dropped even further to 13.7%. Another clinically meaningful way to assess the predictive value was to compare each Face Rank to all Face Ranks below it. Again, as the magnitude of expression of the FAS facial phenotype was reduced, the PPV dropped precipitously. One additional clinically meaningful way to assess the predictive value of the FAS facial phenotype was to dichotomize the 4-point facial Likert scale into a present/absent scale, splitting it in half at different cut-points. For example, using the current definition of the FAS facial phenotype: present equals Rank 4 and absent equals Ranks 1, 2 and 3; the Rank 4 phenotype is 100% predictive of PAE (all children with the Rank 4 Face have a documented PAE). If the 4-Digit Code FAS facial phenotype was relaxed: redefined as present equals Ranks 4 and 3 and absent equals Ranks 2 and 1; the PPV drops to 36.9%. Only 36.9% of subjects with Rank 3 or 4 faces had documented PAE. If the facial phenotype was further relaxed; redefined as present equals Ranks 4, 3 and 2 and absent equals Rank 1; PPV drops to 17.7%. This PPV is essentially identical to the PPV of the Hoyme et al., facial phenotype (17.9%). In a previous study [18], the relaxation of the Hoyme et al., facial phenotype was confirmed to be equivalent to 4-Digit Facial Ranks 2, 3 and 4 combined.

Specificity and PPV for the combined presence of the FAS facial phenotype, growth deficiency and microcephaly

When all three physical features of FAS were present in accordance with the Hoyme et al., 2016 FASD guidelines (the Hoyme et al., FAS facial phenotype, growth deficiency ≤ 10th percentile and OFC ≤ 10th percentile), PPV only reached 52%. Twenty-one children presented with all three physical features (FAS facial phenotype, growth deficiency and small OFC); but only 11 of the 21 had a documented PAE (52% PPV). The presence of all three physical features failed to predict PAE above random chance (50%). Specificity to PAE increased to 99% (all 3 features were absent in 99% of children with no documented PAE).

Specificity and PPV of growth deficiency and microcephaly

The PPV for growth deficiency, even at the most severe level (height and weight ≤ 3rd percentile: Growth Rank 4), never rose above 48.5% (no better than random chance). Only 20 of 41 children with Rank 4 growth deficiency had documented PAE. The PPV for microcephaly (OFC ≤ 3rd percentile) was 36.8%; only 35 of the 95 children with microcephaly had documented PAE. These outcomes were anticipated, as it is well documented in the medical literature that PAE is not the only cause of growth deficiency and microcephaly.

Sensitivity and NPV

Since the majority of individuals with PAE do not present with the Rank 4 FAS facial phenotype, growth deficiency and/or microcephaly, as postulated, sensitivity was quite low. If one used these features to screen for PAE in a population, most individuals with PAE would be missed.

Table 2. How well the FAS facial phenotype, microcephaly and/or growth deficiency predict prenatal alcohol exposure.

FAS Physical Features	N Group1 vs. 2	PPV	95% C.I.	NPV	95% C.I.	Specificity	95% C.I.	Sensitivity	95% CI
4-Digit Face Ranks 4, 3, 2 vs. Rank 1 [A]									
Face 4 vs. 1	20 vs. 776	100		89.6	88.6-90.4	100	99.5-100.0	19.8	12.5-28.9
Face 3 vs. 1	121 vs. 776	26.5	20.2-33.8	89.6	88.4-90.6	88.7	86.2-90.8	28.3	20.2-37.6
Face 2 vs. 1	685 vs. 776	13.7	12.0-15.6	89.6	87.9-91.0	54	51.3-56.8	53.7	46.0-61.3
Each face rank vs. all ranks below[A]									
Face 4 vs. 3,2,1[B]	20 vs. 1582	100		87	86.5-87.4	100	99.7-100.0	8.8	5.5-13.3
Face 3 vs. 2,1	121 vs. 1461	26.5	19.8-34.4	88	87.4-88.6	93.5	92.1-94.8	15.5	10.8-21.2
Face 2 vs. 1	685 vs. 776	13.7	12.0-15.6	89.6	87.9-91.0	54	51.3-56.8	53.7	46.0-61.3
Face Rank Scale Dichotomized[A]									
Face Rank 4 vs. 3,2,1	20 vs. 1582	100		86.9	86.5-87.4	100	99.7-100.0	8.8	5.5-13.3
Face Ranks 3,4 vs. 2,1	141 vs. 1461	36.9	30.0-44.4	88	87.2-88.8	93.5	92.1-94.8	23	17.6-28.1
Face Ranks 2,3,4 vs. 1	826 vs. 776	17.7	16.1-19.3	89.6	87.7-91.2	50.7	47.9-53.2	64.3	57.7-70.6
Face Rank 4 vs. 3,2,1 African Americans excluded	7 vs. 1093	100		88.4	88.0-88.8	100	99.6-100.0	5.2	2.1-10.5
Hoyme 2016 FASD Guidelines[C]									
FAS Face vs. no FAS Face	274 vs. 819	17.9	14.5-21.9	89.7	88.4-90.9	76.6	73.8-79.2	36.8	28.7-45.6
FAS Face + growth ≤ 10%[D]	48 vs. 1045	39.6	27.4-53.2	89.1	84.8-89.8	97	95.7-98.0	14.3	8.8-21.4
FAS Face + OFC ≤ 10%[D]	48 vs. 1029	37.5	25.6-51.1	88.9	88.2-89.6	96.8	95.5-97.90	13.6	8.3-20.7
FAS Face + growth ≤ 10% + OFC ≤ 10% [E]	21 vs. 1075	52.4	32.3-71.8	88.6	88.0-89.1	98.9	98.1-99.5	8.2	4.2-14.2
Hoyme et al., FAS face using UW Lip-Philtrum Guide 1	121 vs. 979	29.8	23.1-37.4	89.9	89.0-90.9	91.2	89.2-92.9	26.9	19.6-35.2
Growth and Microcephaly									
Growth Rank 4 vs. 1	41 vs. 1383	48.8	34.5-63.3	87.9	87.4-88.5	98.3	97.4-99.0	10.7	6.7-16.0
Growth Rank 3 vs. 1	32 vs. 1383	31.3	18.0-48.6	87.9	87.5-88.3	98.2	97.3-99.0	5.7	2.7-10.1
Growth Rank 2 vs. 1	146 vs. 1383	20.6	15.1-27.3	87.9	87.3-88.6	91.3	86.7-92.3	15.2	10.5-21.0
Growth ≤ 3% (Ranks 3,4 vs. 2,1)	73 vs. 1529	41.1	30.9-52.1	87.1	86.5-87.7	96.9	95.8-97.7	13.2	9.1-18.3
Growth ≤ 10% (Growth Ranks 2,3,4 vs. 1)	219 vs. 1383	27.4	22.5-32.9	87.9	87.1-88.8	88.4	86.6-90.1	26.4	20.8-32.7
Growth ≤ 10% African Americans excluded	145 vs. 955	24.1	18.5-30.8	89.6	88.6-90.6	88.6	86.4-90.6	26.1	18.9-34.4
OFC ≤ 3%	95 vs. 1338	36.8	28.3-46.3	83.5	81.4-85.4	95.1	93.7-96.2	16.5	11.8-22.2
OFC ≤ 10%	167 vs. 1264	25.8	20.2-32.2	86.8	86.0-87.6	89.8	88.0-91.5	20.5	15.2-26.6
OFC ≤ 10% African Americans excluded	127 vs. 894	22.8	17.0-30.0	89	88.1-90.0	89	86.8-91.0	22.8	15.9-31.2

A. See Figures 2 and 3 for how growth and face are ranked by the FASD 4-Digit Code.

B. This outcome is portrayed in Figure 1.

C. The study population used to assess the Hoyme et al., FASD criteria does not include African Americans as detailed in the Methods section.

D. Hoyme et al., 2016 FASD guidelines [7] require 2 physical features be present to diagnose PFAS when PAE is unknown (the FAS facial phenotype and growth ≤ 10th percentile or the FAS facial phenotype and OFC ≤ 10th percentile).

E. Hoyme et al., 2016 FASD guidelines require 3 physical features be present to diagnose FAS when PAE is unknown (the FAS facial phenotype and growth ≤ 10th percentile and OFC ≤ 10th percentile).

Abbreviations: CI: confidence interval; NPV: negative predictive value; OFC: occipital frontal circumference (head circumference); PPV: positive predictive value; UW: University of Washington.; vs: versus

As anticipated, NPV was uniformly high (83.5% to 89.6%) across each of the physical features (the FAS facial phenotype, growth deficiency ≤ 10th percentile and OFC ≤ 10th percentile). The absence of one or more features correctly predicted the absence of PAE 83% to 89% of the time. But it is important to remember that NPV is influenced by the prevalence of PAE in the study population. As the prevalence of PAE decreases, the probability of correctly predicting the absence of PAE increases.

Discussion

The observed outcomes in this study were concordant with the postulated outcomes. The Rank 4 FAS facial phenotype, as defined by the FASD 4-Digit Code [3], was the only physical outcome that provided sufficient PPV and specificity to PAE (100%) to allow the facial phenotype to be used as confirmation of PAE in a diagnostic setting when a written or verbal documentation of PAE is not available. Even minimal relaxation of the facial phenotype criteria (e.g., Face Rank 3) resulted in a precipitous decrease in PPV (35%) and specificity (88.7%), rendering the relaxed phenotypes incapable of serving as confirmation of PAE. It is for this reason that the FASD 4-Digit Code requires confirmed PAE for all diagnoses with the exception of FAS. The high PPV and

specificity metrics generated from the current study are consistent with the PPV and specificity metrics generated from our previous studies dating back to 1995 [8,9,20,31].

The FAS facial phenotype as defined by the Hoyme et al., 2016 FASD guidelines resulted in a very low PPV (17.9%) and low specificity (76.6%), both far too low to serve as valid confirmation of PAE in a diagnostic setting when written or verbal confirmation of PAE is unavailable. Requiring the presence of all three physical features of FAS (the Hoyme et al., FAS facial phenotype and growth ≤ 10th percentile and OFC ≤ 10th percentile) did not increase PPV sufficiently to allow the cluster of physical features to serve as diagnostic confirmation of PAE. PPV increased only to 52%. Of the 21 children that presented with all three of these physical features, only 52% had a documented PAE. The presence of all three features predicted PAE no better than chance (50%). It is important not to misinterpret this finding. The low PPV associated with growth deficiency and OFC ≤ 10th percentile does not mean PAE does not cause growth deficiency and microcephaly. The low PPV simply reflects the fact that there are many risk factors (not just PAE) that cause growth deficiency and reduced head circumference, especially in this high-risk foster population. Growth deficiency and microcephaly are strongly correlated with PAE, highly predictive of cognitive/behavioral dysfunction and essential to the diagnosis of FASD [32].

It is important to clarify that high PPV and specificity are required to confirm PAE in a FASD diagnostic setting. Diagnostic evaluations provide definitive information about the presence or absence of a condition or exposure. In contrast, lower levels (~80%) of PPV and specificity may be deemed acceptable in a FASD screening setting, when the goal is to identify individuals at risk for adverse outcomes caused by PAE. In a screening activity, one may be more willing to accept PAE false-positives so as not to miss PAE true-positives. One would expect the false positives to be corrected in the diagnostic phase of a screening. A recent study by Goh et al., [33] serves as a good example of a screening tool developed to determine which children with neurodevelopmental problems were likely to be affected by PAE and require clinical follow-up. The tool screens for different combinations of outcomes (e.g., IQ, measures from the Child Behavior Checklist [34] and Vineland Adaptive Behavior Scales [35], 1 or more of the 3 Hoyme et al., FAS facial features, ptosis, incomplete extension of one or more digits, and growth or head circumference ≤ 10th percentile) in hierarchical fashion to predict PAE. When the screening tool was administered to a group of 454 children, in which 145 (32%) had PAE, the tool performed with the following metrics: PPV = 70.7%, NPV 86.7, specificity 80.6%, and sensitivity 79.2%. The PPV of 70.7% means 29.3% of the children predicted to have PAE, did not have PAE (e.g. 29.3% were false positives, their birth mothers did not drink during pregnancy). A false-positive rate of this magnitude could be deemed acceptable in a screening activity; but would be unacceptable in a diagnostic clinic.

FASD diagnostic guidelines that use relaxed criteria for the FAS facial phenotype risk misdiagnosing and over-diagnosing FAS and partial FAS when PAE is unknown. These misdiagnoses can lead to over-estimates of the prevalence of FAS and PFAS in FASD screening/surveillance activities that target populations where confirmation of PAE is difficult to obtain. For example, May et al., [36] conducted a FASD screening among first grade students in a Midwestern U.S. community. Screen positives received FASD diagnostic evaluations in accordance with the Hoyme et al., [37] criteria that permit diagnosis of FAS and PFAS when PAE is unknown. The relaxed facial, growth and head circumference criteria for FAS and PFAS are identical between the Hoyme et al., 2005 [37] and Hoyme et al., 2016 [7] FASD diagnostic systems. The authors reported alcohol use during the index pregnancy was confirmed in only 33% of the cases diagnosed with FAS and 61% of the cases diagnosed with PFAS. It is unclear what feature(s) were present among two thirds of the FAS cases and one third of the PFAS cases that allowed these diagnoses to be rendered with unknown PAE. The authors concluded *"The prevalence of FAS cases in this study of first grade children in this general population is likely 6 to 9 per 1000. It is significantly higher than older, previously accepted estimates of FAS (0.2 to 3 per 1000) that were generated from less representative samples that did not use active case ascertainment. But these findings are similar to recent rates published for the United States, Italy, and Croatia, 2 to 7 per 1000, which used similar, active methods of case identification and ascertainment. For FAS and PFAS combined, the likely maximum range of rates is 17 to 26 per 1000, and for total FASD, the rates range from 24 to 48 per 1000. Therefore, rates from this study are all well above the old estimate of 1% for total FASD* [38]."

The outcomes of the current study continue to support that the Rank 4 FAS facial phenotype is unique to (caused only by) PAE. Nevertheless, updates in genetic testing technologies such as chromosomal microarray analysis suggest some of the physical and neurobehavioral abnormalities observed in FASD overlap with those observed among individuals with chromosomal disorders. Chromosomal microarray abnormalities occur among 15-20% of individuals with unexplained developmental disability/intellectual disability, autism spectrum disorder and multiple congenital anomalies [39]. Chromosomal abnormalities (often chromosomal micro-deletions or micro-duplications) have been reported in 8-14% of individuals with FASD [39-44]. But to date, these studies have been descriptive, not empirical in design. To empirically confirm chromosomal abnormalities serve as an alternate etiology for the Rank 4 FAS facial phenotype, one would have to identify a sufficiently large group of individuals who present the Rank 4 FAS facial phenotype, have the chromosomal abnormality and have a confirmed absence of PAE. As proffered by Kahila et al., [41], are chromosomal abnormalities an alternate etiology for the physical and neurobehavioral abnormalities observed among individuals with PAE or are the chromosomal abnormalities the consequence of PAE? Halsted et al. [45] suggested that alcohol consumption decreases the amount of folate, which is needed for cells' methionine cycle. Thus, alcohol could reduce the production of methyl groups for DNA and histone methylation, cause hypomethylation, and consequently decrease the stability of the chromosomes [41]. To date, there have been no reports of the Rank 4 FAS facial phenotype present in an individual with chromosomal abnormalities and confirmed absence of PAE.

Study strengths and limitations

Documentation of PAE was both a strength and limitation in this study. PAE is inherently difficult to accurately confirm or rule-out in any population. Due to the stigma associated with drinking

during pregnancy, birth mothers are typically reluctant to report their alcohol use during pregnancy. The most frequent source of confirmation of PAE in the FASDPN clinic is past birth, medical and social service records [46]. It takes time and effort to obtain these records, but in so doing, one is likely obtaining the most accurate record of PAE available. If there is error in the "true exposure" status of a study population, the classification/prediction parameters derived from that "true exposure" classification can be impacted. The strength of this study was the thoroughness with which all records were obtained and reviewed by the foster care program to identify, as accurately as possible, the "true PAE" status of each child.

Conclusion

FASD diagnostic guidelines that use relaxed criteria for the FAS facial phenotype risk misdiagnosing and over-diagnosing FAS and partial FAS when PAE is unknown. These misdiagnoses can lead to over-estimates of the prevalence of FAS and PFAS in FASD screening activities that target populations where confirmation of PAE is difficult to obtain.

Ethical Approval

FASD diagnostic guidelines that use relaxed criteria for the FAS facial phenotype risk misdiagnosing and over-diagnosing FAS and partial FAS when PAE is unknown. These misdiagnoses can lead to over-estimates of the prevalence of FAS and PFAS in FASD screening activities that target populations where confirmation of PAE is difficult to obtain.

Author Contributions

The author was the principal investigator for the original study and conducted all analyses and manuscript preparation for the current study.

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Concerns and Strengths: Caregiver Perceptions of Their Infant/Toddler with Prenatal Alcohol Exposure †

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Abstract: Caregiver-reported assessments provide opportunities for caregivers to share concerns and identify the strengths of their infant/toddler regarding prenatal alcohol exposure (PAE). These insights may reveal under-recognized concerns and inform a strengths-based approach to early intervention. The purpose of this study was to describe the type and frequency of caregiver-reported concerns and strengths in a sample of infants/toddlers at the time of their fetal alcohol spectrum disorder (FASD) diagnostic evaluation. Caregivers' concerns and strengths were identified in the context of two parent-report questionnaires, the Infant Toddler Sensory Profile and Child Behavior Checklist/1$^1/_2$-5. By using content analysis, caregivers' open-ended responses were identified, coded, and analyzed. The frequencies of all the coded concerns and strengths were counted. The data were compared across the two age groups (<2 years and ≥2 years) and caregiver status. Caregivers (n = 117) identified numerous concerns and strengths across multiple categories. The most frequently reported concerns were related to aggressive behavior, language/communication, and sensory processing. The most frequently reported strengths were related to happiness, sociability, and love. The type of concerns and strengths reported were relatively consistent across age and caregiver status. These findings reinforce the value of caregivers' perspectives and offer a reminder to practitioners that infants/toddlers with PAE and their caregivers have many strengths that can be harnessed, in addition to a range of challenges that must be addressed.

Keywords: prenatal alcohol exposure; fetal alcohol spectrum disorder; infant; toddler; strengths; concerns

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1. Introduction

Prenatal alcohol exposure (PAE) can disrupt the neurodevelopmental and behavioral trajectory of infants/toddlers with lasting impacts on learning, mental health, and overall well-being [1,2]. Fetal alcohol spectrum disorder (FASD) is a term used to describe the full range of physical, cognitive, and behavioral impairments caused by PAE, which are estimated to occur in at least 1% of children and youth in the general population [3,4]. Infants/toddlers with PAE are a heterogeneous group of children who may experience a wide range of delays in development, sensory processing, and/or emotional and behavioral functioning [5]. Challenges in any one of these developmental domains can limit participation in everyday routines and activities and negatively influence the quality of parent–child interactions and early relationships [6,7]. Conversely, infants/toddlers with PAE also possess individual strengths and positive attributes [8] that can serve as protective factors and support whole child development.

Early interventions that target risk factors and build on individual strengths can alter the course of development in a positive direction. Findings from decades of developmental and intervention science have demonstrated the substantial benefits of early intervention on child development and family well-being [9]. The first three years of life have

been recognized as an incredibly important time for child development, given the brain's capacity for change and sensitivity to environmental influences [10]. With an emphasis on promoting healthy parent–child interactions and strengthening family adaptation, a family-centered early intervention approach is well-suited to respond to the diverse needs of infants/toddlers with PAE [6,11].

Although early identification and diagnosis may be the best way to positively influence outcomes in young children with PAE [12], PAE appears to be under-recognized by early childhood practitioners [11]. The early identification of infants/toddlers with PAE is complicated in several ways. Challenges by multiple systems of care (i.e., health care, child welfare, early intervention, and infant mental health) to initiate and conduct universal screenings or identification processes for prenatal exposures may be, in part, inhibiting earlier referrals for FASD diagnosis [13]. In addition, not all infants/toddlers with PAE present with easy-to-recognize symptoms, such as characteristic physical findings (e.g., growth problems, FAS facial features, structural brain abnormalities, etc.) or severe neurodevelopmental/behavioral delays [14]. Instead, many infants/toddlers may have more subtle developmental or behavioral indicators [15,16] that are not as easily recognized by early childhood practitioners, thus translating into a missed opportunity for early identification and intervention.

Caregivers, on the other hand, are often the first to raise concerns about their child's development or behavior and can, therefore, serve as a critical step in identifying early delays or problems that may arise from PAE. Directing attention to caregiver-reported assessments, which constitute a valuable component of early childhood assessment, is one way to learn about caregiver concerns. Standardized caregiver-report measures that are commonly used to assess infant sensory processing and behavior provide a way for parents or guardians to examine and report child behaviors. They permit caregivers to express their concerns through rating scales and responses to open-ended questions. Although clinicians tend to focus their attention on rating scale outcomes, using open-ended questions to ask about parent concerns can often lead to responses that are more spontaneous and personal [17]. It is through open-ended questions that new or under-recognized concerns related to PAE may be uncovered, as caregivers provide responses in their own words and are not constrained by predetermined responses [18].

By the nature of their role and relationship, primary caregivers have a unique vantage point that makes them acutely aware of the day-to-day challenges faced by their child. This increased awareness makes caregivers a vital resource for identifying children whose development and behavior do not appear typical. Previous research with caregivers of children with PAE or FASD demonstrates caregivers' vigilance to variations in their child's development and behavior. In a study of 1400 structured interviews of caregivers raising children impacted by PAE, the outcomes confirmed caregivers were highly preceptive in differentiating the cognitive and behavioral challenges of children across the continuum of FASD [19]. In a second study on the foster mothers of children (ages 2–16 years), a multitude of problems was reported, including concerns related to child cognition, behavior management, and coping with the daily realities of life [20]. Likewise, a third study describing the lived experiences of eight birth mothers of a child/ren with FASD (8–30 years) reported cognitive concerns (i.e., problems with attention, comprehension, and memory) and problem behaviors (i.e., excessive crying or no crying, hyperactivity, aggressiveness), in addition to health issues and delayed developmental milestones [21]. A fourth study emphasized the concerns faced by caregivers, including FASD-related stigma, family stress, and a lack of knowledge by professionals [22]. Finally, in a study by Pruner et al. [8], caregivers were asked to reflect on the challenges faced by their children with PAE during their first three years of life. Caregivers reported a diversity of concerns spanning across all domains of development and further reflected on how early interventions met (or did not meet) those needs. Collectively, these studies recognize caregivers' valuable observation skills and insights into their children's developmental needs. In accordance with this, the Academy of Pediatrics recommends that health professionals ask about and

attend to caregiver concerns as a first step toward the developmental surveillance of infants and young children [23,24].

The recent literature has emphasized a need for a strengths-based approach to assessment and intervention regarding children with FASD [25,26]. Guiding caregivers to identify child strengths during a clinical encounter can extend benefits to both caregivers and practitioners [27]. A strengths-based approach can offer parents a sense of hope, alleviate child-related stress, and strengthen parenting capacity [28–30]. When early childhood practitioners appreciate the variety of child strengths identified by caregivers in this population, it may enable them to recognize and celebrate these assets more easily and in partnership with caregivers. In a parallel process, a strengths-based approach can enhance the bond between the practitioner, the caregiver, and the child, thus building effective working relationships and perhaps reducing FASD-related stigma [28,31,32]. To this end, 20 years of caregiver surveys of patients diagnosed with FASD at the University of Washington Fetal Alcohol Syndrome Diagnostic and Prevention Network (FASDPN) clinic confirmed that caregivers were highly satisfied with the strength-based approach to assessment and intervention [33].

Understanding the types of strengths and positive attributes of infants/toddlers with PAE from the perspective of their caregivers can inform strengths-based interventions. While an extensive amount of research has documented the challenges and impairments experienced by individuals with FASD across their lifespan, less research has focused on identifying strengths at any age [26,34]. Four studies were identified that described caregiver perceptions of child strengths. One study found that the caregivers of children aged 5–21 years recognized many positive traits (i.e., friendliness, hard-working, compassion, etc.) and abilities (e.g., artistic, athletic, etc.) in their child [35]. A second study identified the relative strengths in personal selfcare and household chore activities compared with other adaptive skills for children ages 5–8 years [36]. Third, the caregivers of school-age children reported a range of personal strengths in the context of students' educational experiences, describing their child as being artistic, having strong verbal skills. or having good work habits [37]. In a fourth study, all caregivers were eager to share what they enjoyed most about their child during the early intervention period, including moments of affection, love, and laughter [8]. Notably, Olson and Montague [38] reported the strengths of young children with FASD based on informal reports, which "are filled with descriptions of how engaging, innocent, straightforward, amusing, curious and social young children with an FASD can be". When taken together, these studies and informal reports highlight caregivers' awareness of child strengths and their willingness to communicate these strengths to others.

The present study was designed to address the following questions: (1) What are the concerns and strengths reported by caregivers regarding their infant/toddler (ages 7–42 months) with PAE? (2) From a descriptive perspective, do there appear to be patterns between caregiver types (birth parent, foster/adoptive parent, or other biological relatives) or child age (less than 2 years or 2 years and older) and the type or frequency of reported concerns and strengths? Examining caregiver-reported concerns may yield useful information regarding delays in child development or problem behaviors that warrant the attention of practitioners, signal the need for diagnostic referral, and/or lend important insight into the impact of these concerns on families. Understanding how child age or caregiver status can influence the reporting of concerns may facilitate a more targeted approach for practitioners when inquiring about caregiver concerns and for knowing what kinds of child development information and education certain families might need. In addition, the identification of child strengths and positive characteristics can provide opportunities to enhance parent–child interactions, incorporate these strengths into interventions, and help build caregiver-practitioner partnerships.

2. Materials and Methods

The data for the current study were collected as part of a larger retrospective chart review of diagnostic assessment data from 125 infants/toddlers seen at the University of Washington FASDPN clinic between 2009 and 2019. This clinic does not require patients to present with a concern or delay, only a confirmed PAE at any level. Two linked studies were generated from this chart review, including (1) a descriptive study that examined the developmental, sensory processing, and behavioral outcomes of infants/toddlers with PAE [5]; and (2) the current study, which described caregivers' early concerns and perceptions of their infant/toddlers' strengths, based on data from two standardized caregiver questionnaires, the Infant/Toddler Sensory Profile (ITSP), and the Child Behavior Checklist/1½-5 (CBCL). All study activities were conducted with the University of Washington Human Subjects approval and caregiver consent at the time of their child's FASD diagnostic evaluation.

2.1. Participants

Caregivers were included in this study if their infant/toddler met the inclusion criteria for the prior study [5] and they completed the ITSP questionnaire and/or the CBCL as part of their child's FASD diagnostic evaluation. Child inclusion criteria for the first study were as follows: (1) age 1 month to 3.5 years—at the time of their FASD diagnostic evaluation; (2) received one of the following FASD 4-Digit Code diagnostic classifications (diagnostic categories A–C, D–J) reflecting the full continuum of outcomes observed among individuals with prenatal alcohol exposure (a) fetal alcohol syndrome (FAS; A,B) or partial fetal alcohol syndrome (PFAS; C), (b) static encephalopathy/alcohol exposed (SE/AE; E,F), (c) neurobehavioral disorder/alcohol exposed (ND/AE; G,H), (d) sentinel physical findings/alcohol exposed (I), or (e) no physical findings or central nervous system (CNS) abnormalities detected/alcohol exposed (Normal CNS/AE; (J) (see [39] for details about the FASD 4-Digit Diagnostic Code and [5] for detailed demographics of the prior study sample); and (3) had complete data on at least two domains of the Bayley Scales of Infant and Toddler Development (Bayley-III, [40]). Standardized parent questionnaires were completed by the primary caregiver prior to the scheduled diagnostic clinic date. Time, effort, or other demands placed on a caregiver may have resulted in some caregiver-report measures (i.e., Bayley-III Social-Emotional and Adaptive Behavior domains, ITSP, and CBCL) not being fully completed.

2.2. Measures

The data for this study were collected as part of a standard intake and diagnostic process for the FASDPN diagnostic clinic visit. The measures used for this study are described below.

Infant Toddler Sensory Profile (ITSP [41]). The ITSP is a 48-item caregiver questionnaire that measures sensory modulation abilities in daily life for infants/toddlers (7–36 months). Caregivers rate the frequency of infant/toddler sensory behaviors on a 5-point Likert scale. Caregivers also have the opportunity to respond to two open-ended questions: "What do you see as your child's strengths?" and "What are your concerns?". It is relevant to note that infants/toddlers older than 36 months were administered the Short Sensory Profile (SSP; [42]), which does not have open-ended questions as part of the questionnaire. Therefore, caregivers of infants/toddlers older than 36 months were included in this study if they completed the Child Behavior Checklist 1½–5 years only.

Child Behavior Checklist 1½–5 years (CBCL [43]). The CBCL is a 100-item caregiver questionnaire used to identify a range of emotional and behavioral problems in young children ages 1.5–5 years. Caregivers use a rating scale to determine the presence or absence of emotional and behavioral problems based on the preceding 2 months. Caregivers also have the opportunity to respond to two open-ended questions: "What concerns you most about your child?" and "Please describe the best things about your child".

2.3. Descriptive Information for Participants

Three salient features from the FASD 4-Digit Diagnostic Code used in this study are briefly described below. See [39] for a more comprehensive description of these diagnostic features.

The FASD 4-Digit Diagnostic Code generates the following clinical diagnoses. FAS, PFAS, SE/AE, ND/AE, Sentinel Physical Findings/AE; No Physical or CNS Abnormalities/AE.

Central Nervous System (CNS) Functional Rank. Rank 1 = no dysfunction; Rank 2 = mild-to-moderate dysfunction; Rank 3 = severe dysfunction [39]. CNS functional ranks 1–3 document the severity of CNS dysfunction and are based on brain function (executive function, memory, cognition, social/adaptive skills, academic achievement, language, motor, attention, and activity level) assessed by an interdisciplinary team using standardized psychometric tools.

Postnatal Risks. Rank: 1 = no risk; 2 = unknown risk; 3 = some risk; and 4 = high risk) [39]. Individuals with PAE often present with a multitude of postnatal risks that could also be adversely impacting their development. Postnatal risk factors documented in the FASDPN database include perinatal complications, number of home placements, physical and/or sexual abuse, neglect, and trauma. The ranking is determined by clinical judgment at the time of the FASD evaluation and is based on available records and caregiver or other reports on intake forms and/or clinical interviews.

2.4. Data Analysis Plan

This study used a directed content analysis approach [44] to identify, categorize, and describe all instances of concerns and strengths reported by caregivers at the time of their child's diagnostic evaluation. The directed approach begins with a framework for collecting and analyzing the data but allows for new insights to emerge through a process of inductive category development [43]. In this study, researchers aimed to validate an existing framework (domains commonly assessed in early childhood) in a new context (describing caregivers' concerns and strengths). When the data did not fit into the existing framework, new categories were added to capture all possible instances of caregiver concerns and strengths [44,45].

The written responses to the two questions from the ITSP and two questions from the CBCL were extracted verbatim, excluding any identifying information. A coding system was developed that had multiple levels. First, responses were separated into two groups based on question type—concerns versus strengths/best things. Next, the researchers read all the caregiver comments related to concerns and organized the responses into broad categories. These broad categories arose from the data to reflect general areas of function or development (i.e., Development, Behavior, General/Medical, and Caregiving). After the data related to concerns were sorted, the data within each broad category were analyzed further to create subcategories reflecting the different examples of concerns within each broad category. Some of these subcategories were based on domains commonly assessed in early childhood or contained within the ITSP or CBCL measures, while others arose from the data (these are identified in Appendix A). A similar analysis was conducted with the strengths/best things data, with the broad categories being Development, Personality Traits, Interests, and Caregiving, and the subcategories within each of these are reported in Appendix B.

Two researchers (MP, JM) separately coded 50% of caregiver responses using the initial coding systems. They compared their results, and any discrepancies with how well the categories fit the data were discussed, and adjustments to the category structure were made. This process was repeated until consensus was reached, and all of the data total responses were coded. Once the coding systems were finalized, the first author coded the remaining responses.

Frequency counts for each coded category were calculated. Responses that were left blank or completed with statements such as "no concerns at this time" or "none" were also tracked. When a response contained multiple words or phrases that were suggestive

of a concern/strength, it was only coded once. For example, the description "my child is extremely social, charming and loves other kids", was coded under Sociability one time. On the few (n = 10) occasions that a response fell under two categories, the response was coded twice. For example, the description "doesn't seem to understand" was coded under the two categories of Cognitive and Language concerns because the reason for the comprehension problems was not specified (i.e., whether it was a cognitive or language problem). Another example, "my child is easily over-stimulated", was coded under the two categories of Regulatory and Sensory Processing because of the overlapping nature of this concern. When a caregiver completed both measures and shared similar concerns or strengths on both questionnaires, the responses were coded only one time. As a last step, the quantitative data were descriptively compared across age groups (i.e., <2 years and ≥2 years of age) and caregiver status (i.e., biological parent, foster/adoptive parent, other biological family).

3. Results

Records from 117 caregivers of infants/toddlers with PAE (ages 7–42 months) met the inclusion criteria for this study. Of these caregivers, 32% were birth parents, 44% were foster/adoptive parents, and 25% were extended relatives of the child (e.g., grandparent, aunt). An overwhelming majority of the sample (91%) presented with at least some level of postnatal risk in addition to their PAE. A total of 80% percent of caregivers in the sample completed the ITSP (7–36 months), while 57% completed the CBCL (1.5–3.5 years). See Table 1 for participant characteristics.

Table 1. Demographic and clinical characteristics of the 117 participants.

Caregiver and Child Characteristic	N	(Valid %)
Respondent		
Biological mother	34	(29.1)
Biological father	3	(2.6)
Other biological family member	29	(24.7)
Foster parent	44	(37.6)
Adoptive parent	7	(6.0)
Total caregiver sample size	**117**	
Completed ITSP	94	(88.7)
Eligible to complete ITSP	106	
Completed CBCL	67	(82.7)
Eligible to complete CBCL	81	
Completed both ITSP & CBCL	54	(46.2)
Age of child described (years)		
0.5 to 0.99	14	(12.0)
1–1.99	45	(38.4)
2–2.99	44	(37.6)
3–3.5	14	(12.0)
Mean (SD)	1.99	(0.78)
Sex of child at birth		
Female	60	(51.3)
Male	57	(48.7)
FASD Diagnosis (Diagnostic category)		
FAS	3	(2.6)
PFAS	4	(3.4)
SE/AE	13	(11.1)
ND/AE	72	(61.5)
Sentinel physical findings/AE	5	(4.3)
No sentinel physical findings or CNS abnormalities detected/AE	20	(17.1)

Table 1. *Cont.*

Caregiver and Child Characteristic	N	(Valid %)
CNS Functional Rank		
Rank 1, no dysfunction	27	(23.1)
Rank 2, moderate dysfunction	86	(73.5)
Rank 3, severe dysfunction	4	(3.4)
Postnatal Risk: Rank		
1. No risk	10	(8.5)
2. Unknown risk	1	(0.9)
3. Some risk	69	(59.0)
4. High risk	37	(31.6)

Notes: Infant toddler sensory profile 7–36 months (ITSP); child behavior checklist 1.5–5 years (CBCL); fetal alcohol spectrum disorder (FASD); fetal alcohol syndrome (FAS); partial FAS (PFAS); static encephalopathy/alcohol-exposed (SE/AE); neurobehavioral disorder/alcohol-exposed (ND/AE).

3.1. Concerns Identified

The coding process used for this study generated a list of 19 unique concerns expressed by caregivers (Appendix A). Caregivers reported an average of 2.5 concerns per child, ranging from 0–7 concerns per child. A total of 293 concerns were reported across the study sample. The five most frequently reported concerns were related to developmental and behavioral challenges and included aggressive behavior (27%), language/communication (22%), sensory processing (21%), internalizing problems (19%), and regulation (18%). Twenty-four (24%) caregivers did not report a concern for their child for either measure. The proportion of caregivers who did not report a concern was comparable across all three caregiver groups. The frequency of reported concerns across categories is presented in Table 2.

Table 2. Prevalence of reported concerns.

		Age Bands		Caregiver Type		
Category	Total Sample (n = 117) n (Valid %)	<2 Years (n = 59) n (Valid %)	≥2 Years (n = 59)	Birth Parent (n = 33)	Foster/Adoptive Parent (n = 56) n (Valid %)	Other Biological Family (n = 27)
Developmental Concerns						
Overall development	12 (10.3)	10 (16.9)	2 (3.4)	2 (5.7)	7 (12.5)	3 (11.5)
Cognitive	14 (12.0)	5 (8.5)	9 (15.5)	3 (8.5)	7 (12.5)	4 (15.4)
Language/Communication	**26 (22.2)**	9 (15.3)	**17 (29.3)**	**6 (18.2)**	**14 (25.0)**	**7 (26.9)**
Motor	13 (11.1)	**12 (20.3)**	1 (1.7)	5 (14.3)	4 (7.1)	3 (11.5)
Social-emotional						
Regulation	**21 (17.9)**	11 (18.6)	10 (17.2)	1 (2.9)	13 (23.2)	1 (3.8)
Attachment	7 (6.0)	3 (5.1)	4 (6.9)	1 (2.9)	2 (3.8)	1 (3.8)
Adaptive Behavior	9 (7.7)	4 (6.8)	5 (8.6)	1 (2.9)	4 (7.1)	3 (11.5)
Sleep	9 (7.8)	7 (11.9)	2 (3.4)	1 (2.9)	4 (7.1)	1 (3.8)
Eating/feeding	15 (12.8)	9 (15.3)	6 (10.3)	2 (5.7)	8 (14.3)	2 (7.7)
Behavior Concerns						
Internalizing problems	**22 (18.8)**	11 (18.6)	**11 (19.0)**	2 (5.7)	13 (23.2)	5 (19.2)
Externalizing problems						
Attention problems	12 (10.3)	7 (11.9)	5 (8.6)	5 (14.3)	4 (7.1)	5 (19.2)
Aggressive behavior	**32 (27.4)**	**15 (25.4)**	**17 (28.8)**	**7 (20.0)**	**19 (33.9)**	**7 (26.9)**
Sensory Processing	**24 (20.5)**	**14 (23.7)**	10 (17.2)	4 (11.4)	**14 (25.0)**	**6 (22.2)**
Behavioral inflexibility	11 (9.4)	4 (6.8)	7 (12.1)	1 (2.9)	8 (14.3)	2 (7.7)
Safety awareness	11 (9.4)	4 (6.8)	7 (12.1)	1 (2.9)	5 (9.4)	4 (15.4)
Child Concerns (in general)						
PAE & Other Drug Exposures	16 (13.7)	9 (15.3)	7 (12.1)	**8 (22.9)**	4 (7.1)	3 (11.5)
FAS Physical Findings	10 (8.5)	6 (10.2)	4 (6.9)	1 (2.9)	4 (7.1)	5 (19.2)
Physical or health problems	12 (10.2)	9 (15.3)	3 (5.2)	3 (8.5)	7 (12.5)	2 (7.7)
Caregiving Experience	17 (14.5)	6 (10.2)	7 (12.1)	5 (14.3)	8 (14.3)	3 (11.5)
No concerns reported	28 (23.9)	16 (27.1)	13 (22.4)	10 (30.3)	11 (31.4)	7 (26.9)

Notes. Bolded numbers indicate the top 5 (total sample) or the top 3 concerns (age and caregiver categories).

Concerns were explored across age groups. For younger infants/toddlers (<2 years), the caregiver concerns expressed most often were aggressive behavior (25%; *screams at high pitches; extreme temper*), sensory processing behaviors (24%; *sensitivity to sounds, lights,*

and clothes), and motor skills (20%; *isn't sitting up on his own*). For older infants/toddlers (≥2 years), caregivers reported the most concerns with language/communication skills (29%; *slow speech; doesn't talk in more than three-word sentences*), aggressive behavior (29%; *can throw a fit that lasts for some time*) and internalizing problems (19%; *whiny, fussy, and sudden mood changes*). Notably, aggressive behaviors were reported with the most frequency across both age groups.

Concerns across caregiver status were also explored. Birth parents had the most concerns for PAE and other drug exposures (23%; *he was born addicted*), aggressive behavior (20%; *abusive*), and language/communication (18%; *worried about speech development*). The most common concerns reported by foster/adoptive parents were aggressive behavior (34%; *head butts, pulls out gobs of her own hair and even tries to pull mine out*), language /communication (25%; excessively repeats herself, doesn't talk in more than three-word sentences), and sensory processing behaviors (26%; *has extremes in responses to stimuli*). The top concerns noted among other biological family members were language /communication (27%; *speech; constant chatter*), aggressive behavior (27%; *tantrums that are hard to calm down from*), and sensory processing (22%; *becomes inconsolable as soon as caregiver . . . introduces new sensation*). Aggressive behaviors were a top concern that was common across all three caregiver types.

3.2. Strengths Identified

The coding process generated a list of 20 unique strengths (Appendix B). Caregivers identified an average of 3.0 perceived strengths per child, ranging from 0–7 coded strengths each. A total of 352 strengths were coded across the study sample. The most frequent strengths or best things reported were reflective of personality traits: happiness (33%), sociability (30%), love/loving (28%), and curiosity (26%), and for developmental competencies, cognitive ability (22%). In contrast, strengths related to adaptive behavior (1%), eating/feeding (3%), and regulation (3%) were rarely reported. Strengths in the child's interests (14%) and caregiver experience (3–5%) categories were also endorsed less frequently. A total of 25% of caregivers did not report a strength for either measure. The proportion of caregivers who did not report a strength was comparable across all three caregiver groups. Table 3 shows the frequency of reported strengths across categories.

Perceived strengths were explored across two age bands. For infants/toddlers (<2 years), caregivers frequently reported the following personality traits: curiosity (37%; *observant; curious*), happiness (31%; *very happy; happy most of the time*), and love/loving (29%; *child is lovable*). For older infants/toddlers (2–3.5 years), many caregivers described their child as happy (35%; *very happy girl*), social (35%; *loves to interact with me and other children*) and love/loving (30%; *very loving*).

Perceived strengths were also explored across caregiver status. Birth parents reported the most child strengths in the categories of happiness (27%; *happy baby*), love/loving (24%; *she is so loving*), and sociability (21%; *he's a charmer*). Likewise, the most common strengths reported by foster/adoptive parents were happiness (43%; *she brings a lot of happiness to our lives*), sociability (32%; *friendly and outgoing*), and love/loving (27%; *loves her siblings*). The strengths expressed most often by other biological family members were love/loving (37%; *loving boy*), sociability (33%; *her smile and ability to get along with others*), and curiosity (33%; *tries everything, observant*). Sociability and love/loving were perceived strengths common across all three caregiver types.

Table 3. Prevalence of reported strengths or best things.

		Age Bands		Caregiver Type		
Category	**Total Sample (*n* = 117) *n* (Valid %)**	**<2 Years (*n* = 59) *n* (Valid %)**	**≥2 Years (*n* = 58)**	**Birth Parent (*n* = 33)**	**Foster/Adoptive Parent (*n* = 56) *n* (Valid %)**	**Other Biological Family (*n* = 27)**
Developmental Competencies						
Cognitive	**26 (22.2)**	12 (20.3)	13 (22.4)	5 (15.1)	14 (25.0)	6 (22.2)
Language/Communication	11 (9.4)	7 (11.9)	4 (6.9)	1 (3.0)	8 (14.3)	2 (7.4)
Motor/Movement	12 (10.3)	7 (11.9)	5 (8.6)	3 (9.1)	5 (8.9)	4 (14.8)
Social-emotional						
Regulation	3 (2.6)	3 (5.1)	0	1 (3.0)	2 (3.6)	0
Attachment	12 (10.3)	9 (15.3)	3 (5.2)	3 (9.1)	8 (14.3)	1 (3.7)
Adaptive Behavior	1 (0.9)	1 (1.7)	0	0	0	1 (3.7)
Eating/feeding	4 (3.4)	3 (5.1)	1 (1.7)	1 (3.0)	1 (1.8)	2 (7.4)
Personality Traits						
Happiness	**38 (32.5)**	**18 (30.5)**	**20 (34.5)**	**9 (27.3)**	**24 (42.9)**	5 (18.5)
Love/loving	**33 (28.2)**	**17 (28.8)**	**16 (29.6)**	**8 (24.2)**	**15 (26.8)**	**10 (37.0)**
Kindness	25 (21.4)	10 (17.0)	15 (25.9)	6 (18.2)	14 (25.0)	6 (22.2)
Affectionate	10 (8.5)	7 (11.9)	3 (5.2)	3 (9.1)	7 (12.5)	0
Humor	23 (19.7)	12 (20.3)	11 (19.0)	7 (21.2)	11 (19.6)	5 (18.5)
Sociability	**35 (29.9)**	15 (25.4)	**20 (34.5)**	**7 (21.2)**	**18 (32.1)**	**9 (33.3)**
Curiosity	**30 (25.6)**	**22 (37.2)**	8 (13.8)	7 (21.2)	13 (23.2)	**9 (33.3)**
Courage	15 (12.8)	8 (13.6)	7 (12.1)	4 (12.1)	5 (8.9)	6 (22.2)
Autonomy	12 (10.3)	9 (15.3)	3 (5.2)	3 (9.1)	4 (7.1)	6 (22.2)
Zest	18 (15.4)	6 (10.1)	12 (20.7)	6 (18.2)	6 (10.7)	6 (22.2)
Adaptable	19 (16.2)	13 (22.0)	6 (10.3)	4 (12.1)	13 (23.2)	2 (7.4)
Child Interests	16 (13.7)	7 (11.9)	9 (15.5)	4 (12.1)	10 (17.9)	1 (3.7)
Caregiver's Experience						
Confidence with parenting	3 (2.6)	2 (3.4)	1 (1.7)	1 (3.0)	2 (3.6)	0
Appreciation for positive change	6 (5.1)	2 (3.4)	4 (6.9)	0	5 (8.9)	1 (3.7)
No strengths reported	23 (19.7)	12 (20.3)	11 (19.0)	7 (21.2)	10 (17.9)	5 (18.5)

Notes. Bolded numbers in the total sample column indicate the top 5 concerns, and bolded numbers in age and caregiver columns indicate the top 3 concerns.

4. Discussion

In this retrospective study of clinical data, the caregivers of infants/toddlers with PAE described a diversity of concerns and strengths in the context of two developmental questionnaires administered as part of their child's FASD diagnostic evaluation. Our primary findings were that (a) caregivers' predominate concerns fell into the categories of aggressive behavior and language/communication, while sensory processing and internalizing behaviors were also commonly reported; (b) the caregiver-perceived strengths spanned across numerous categories, with positive personality traits related to happiness, sociability, and love expressed most often, and (c) the type and frequency of reported concerns and strengths were relatively consistent across age and caregiver status. The findings from this study recognize the value of caregivers' perspectives and offer an important reminder to practitioners that infants/toddlers with PAE and their caregivers have strengths that can be harnessed, in addition to a range of challenges that must be addressed.

Caregivers reported a broad array of concerns, reflecting the diversity of neurodevelopmental and behavioral outcomes known to be associated with PAE during early childhood [46,47]. Aggressive behaviors such as kicking and screaming, head banging, and prolonged temper tantrums raised the most concerns across both age groups and were relatively consistent across caregiver groups. Previous studies that examined behavior functioning found greater negative effects among infants [1] and preschool-age children with PAE [48,49], as well as a difficult temperament [50] and conduct-based problems [51] among preschoolers. Caregivers' frequent concerns about language/communication are substantiated by studies that described delayed language abilities in infants with PAE [52–54]. Atypical sensory processing behaviors and internalizing problems were commonly described by caregivers in this study and, likewise, have been reported in the literature among infants/toddlers with PAE [15,55–57]. Concerns related to selfregulation, such as difficulty soothing or sleep complaints, were also consistent with selfregulatory difficulties seen in this population [58].

Overall, it appears that caregivers raised concerns that correspond closely to the outcomes from the standardized measures of development, sensory processing, and behavior in the existing literature. The findings demonstrate that caregivers can be an important source of information regarding their children. Explicitly asking caregivers about their concerns may aid in the earlier identification of delays or problems that may arise from PAE, especially when incorporated into an early routine screening or comprehensive clinical assessment [23].

Although most caregiver-reported concerns were coded using the categories from the core developmental domains, ITSP, and CBCL scales, there were a few exceptions. For example, concerns related to parenting were identified by 15% of caregivers, yet the ITSP or CBCL did not explicitly prompt caregivers to consider these concerns. Along the same lines, other concerns (e.g., PAE and other drug exposures and physical and health problems) were reported that were not captured on the questionnaires caregivers had previously completed. While many caregivers' developmental, behavioral, and clinical concerns would have been assessed and/or detected at the time of their child's FASD diagnostic evaluation, it is possible that the concerns related to parenting may have been missed if it were not for the open-ended questions. Caregivers who are struggling with the day-to-day stressors of raising an infant/toddler with PAE often require additional support to engage in sensitive and responsive parenting. With this goal in mind, these findings offer a reminder to practitioners that a combination of assessment approaches is needed to ensure that caregivers have more than one avenue to share concerns. Practitioners need to understand the complex problems facing caregivers, as well as their priorities and desired outcomes, to design treatment plans that are congruent with caregiver goals.

An overwhelming majority of caregivers (88%) shared one or more strengths/best things about their infant/toddler. Happiness, sociability, and love were the strengths reported most often, suggesting many caregivers believed these personality traits were worth knowing about and communicating with others. The finding that caregivers endorsed happiness and sociability among their top two strengths is consistent with a large meta-analysis examining the benefits of frequent positive affect in individuals across multiple life domains, which found happiness to be positively correlated with sociability [59]. Based on previous research on parents of neurotypical children (ages 3–9), love was also a frequently endorsed character trait [60]. For early childhood practitioners, this is useful information for initiating a working relationship with all types of caregivers, regardless of the child's age. Recognized strengths, such as happiness, sociability, and love, may be perceived as a healthy indicator of parent–child connectedness and a starting point for noticing and exploring these perceptions, which is especially important for family-centered care and relationship-focused approaches [61,62]. Alternatively, when caregivers struggle to identify strengths in their child, this may signal to practitioners a need to promote attuned and positive exchanges between caregiver and child. A strengths-based approach is particularly important given the stigma associated with FASD. Both the biological, as well as nonbiological parents of children with PAE experience stigmatization when they are perceived as responsible for their child's negative behavior or delayed development [32]. Cultivating child and caregiver strengths is in alignment with guiding principles of early intervention practice [9], as well as practice guidelines specific to families impacted by substance use [63]. Elevating strengths-based approaches for young children with known or suspected PAE and focusing on child strengths may work towards reducing stigma among caregivers and foster earlier identification and intervention as critical protective factors as early in life as possible [64].

Caregivers identified a few characteristics in both a positive and negative light. For example, the personality trait "zest" was reported by 16% of caregivers when they used phrases such as "my child's personality is larger than life" or "he's a firecracker". In contrast, it appeared some caregivers perceived their child's high energy and excitement as a problem related to attention or hyperactivity (i.e., she is very driven . . . very hyperactive, causing her to fall or run into things often). Furthermore, caregivers reported sociability

as frequent strength, yet they also identified language/communication problems as a frequent concern. While concerns related to the use of language/communication are fundamentally different than the personality trait of sociability, practitioners can play a role in leveraging a child's strong social skills toward the goal of developing language and communication skills. Indeed, building on strengths to compensate for child difficulties is a central intervention principle used with families raising children with FASD [65].

The following are study limitations. Since this was a retrospective chart review, the data were limited to the written responses reported on the assessment forms. As such, we were not able to probe for further detail or ask for clarification about any of the caregiver responses or follow up with those who did not respond. Responses to these questions were optional, and thus there may be bias or differences among caregivers who responded to the open-ended questions compared with those who did not. Caregivers of all types reported strengths and challenges on both measures; however, we cannot generalize results to all young children with PAE and caregivers due to the inherent limitation of a clinical sample. In order to gain a more thorough understanding of caregivers' concerns and child strengths, future research should use a more systematic approach, such as guided interviews or focus groups that pose similar open-ended questions, with the opportunity to ask directed questions about strengths and challenges so that all participants have an equal ability to respond.

5. Conclusions

Caregivers identified concerns that warrant the attention and action of early childhood providers, demonstrating their attunement to the early challenges faced by their children. Caregivers also perceived their children to have many strengths across multiple areas. These findings suggest the importance of understanding the range of concerns and strengths that caregivers perceive in their day-to-day interactions with their children, which can enhance the development of family-centered interventions, strengthen parent–child connectedness, and build effective working relationships between early childhood practitioners and families impacted by PAE.

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Appendix A. Final Coding System Documenting 19 Unique Concerns

Table A1. Final Coding System Documenting 19 Unique Concerns.

Broad Categories	Subcategories	Definition	Example(s)
Development	Overall Development	Concerns with development in general	Child is developmentally behind despite interventions
	Cognitive *	Concerns with comprehension, intelligence, and learning	Slow processing, doesn't know shapes, colors, or letters
	Language/Communication *	Concerns with speech, language, receptive/expressive and social communication	She can't express what she wants, babbles like an infant

Table A1. *Cont.*

Broad Categories	Subcategories	Definition	Example(s)
	Motor/Movement *	Concerns with fine and gross motor skills, movement	Not walking, doesn't sit up
	Social-emotional *		
	Regulation	Difficulty coping with discomforting emotions	Cannot quiet or calm self, easily over-stimulated
	Attachment	Difficulty bonding, seeking comfort and closeness	Difficulty bonding, when's he's away from us he won't engage in play
	Adaptive behavior *	Concerns related to activities of daily living	Baths don't go well, hard time participating in everyday, normal activities
	Sleep	Sleep-related disturbances	Can't fall asleep, only sleeps 2 h at a time
	Eating/feeding	Concerns with feeding, eating, mealtimes	Reflux, poor eating habits, gagging
Behavior	Internalizing problems **	Emotionally reactive, anxious/depressed, somatic complaints and withdrawn behaviors	Quick switches between fury and happy, fussy
	Externalizing problems **		
	Attention problems	Problems with inattention, hyperactivity, or impulsivity	Unable to sit still or focus, frequently trips over objects
	Aggressive behavior	Problems managing frustration, may hurt others or self	Head banging, kicking, prolonged tantrums, screaming
	Sensory processing ***	Sensory behaviors that interfere with daily life	Sensitive to sound, high pain tolerance, doesn't respond to name
	Behavioral inflexibility	Difficulties adapting to changes in routine	Does NOT have transitioning skills, needs a structured environment
	Safety awareness problems	Lack of safety awareness	Will walk off with stranger, fearless, impulsive
General/Medical	Prenatal alcohol & other drug exposures	Concerns related to PAE & other drugs	I drank frequently when pregnant and chewed tobacco
	FAS physical findings	Concerns related to growth deficiency, microcephaly, or FAS facial features	Small size, poor weight gain, small head, thin lip
	Physical or health problems	Concerns related to physical or health problems	Failure to thrive, low muscle tone, born premature
Caregiving	Caregiving concerns	Concerns related to parenting, questions that arise and perceptions about their child's future	Exhausted, worry that child will be unable to catch up with peers, why is he delayed, it's hard to tell if this is normal for his age

Notes. * Categories based on the Bayley-III domains; ** Categories based on the CBCL scales; *** Category based on the ITSP.

Appendix B. Final Coding System Documenting 20 Unique Strengths or Best Things

Table A2. Final Coding System Documenting 20 Unique Strengths or Best Things.

Broad Categories	Subcategories	Definition	Example(s)
Development	Cognitive *	Capacities related to intelligence and learning	Smart, bright, problem-solver
	Language/Communication *	Capacities related to speech, language, receptive/expressive, and social communication	Strong communicator, voices' own opinion
	Motor *	Capacities related to motor skills and movement	Loves to run, athletic, strong
	Social-emotional *		

Table A2. *Cont.*

Broad Categories	Subcategories	Definition	Example(s)
	Regulation	Capacities related to coping with discomforting emotions	Selfsoothes, loves to be cuddled, and really likes deep pressure
	Attachment	Capacities related to bonding, seeking comfort and closeness	Hooked on mama, devoted to brother
	Adaptive behavior *	Capacities related to everyday tasks and activities of daily living (bathing, grooming, toileting, sleep, etc.).	likes to put shoes and socks on by herself
	Eating/feeding	Capacities related to feeding, eating, drinking, and mealtimes	Loves food, not afraid to try different foods
Personality Traits	Happiness	Always happy, joyful, cheerful	Happy child
	Love/loving	Loving and lovable	Very loving
	Kindness	Eager to help and give to others, compassionate	Caring, gentle with younger brother
	Affectionate	Expressing fondness for others	Gives kisses, loves snuggling
	Humor	likes to laugh and bring smiles to others	Jokester, always smiling and laughing
	Sociability	Social engagement and competence	Charming, outgoing, friendly
	Curiosity	Explores and is interested in trying new things	Inquisitive, observant
	Courage	Brave, perseverance, resilient	Fearless, very determined and persistent
	Zest	Approaching life with energy and excitement	Enthusiasm, larger than life, firecracker
	Adaptable	Adapts well, patient, compliant	Mild-tempered, easy going
Interests	Child interests	Interests that capture the child's attention, motivating activities	she loves animals and art, loves to be outside
Caregiving	Confidence with parenting	Responses that show a caregiver's confidence with parenting and knowing their child	we've gotten used to the things he doesn't like; child responds well to structure
	Appreciation for positive change	Responses that show appreciation for child and positive changes	great to have in my life, seems to be progressing

Notes. * Categories based on the Bayley-III domains.

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Research Article

Washington and Alaska Statewide Fetal Alcohol Spectrum Disorder Diagnostic Clinical Networks: Comparison of Three Decades of 4-Digit Code Diagnostic Outcomes and Prenatal Alcohol Exposure Histories

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ABSTRACT

Background: Fetal Alcohol Spectrum Disorder (FASD) screening, diagnosis, intervention, research and prevention hinges on establishment of interdisciplinary FASD diagnostic clinics using an evidence-based method of diagnosis. In 1993, Washington State opened the first interdisciplinary FASD diagnostic clinic sponsored by the CDC as a FASD primary prevention study. Clinic data was used to develop the evidence-based FASD 4-Digit Diagnostic Code, paving the way for the clinic's expansion into a Statewide network of FASD diagnostic clinics (Washington Fetal Alcohol Syndrome Diagnostic & Prevention Network), now in its 30th year. Alaska adopted this Washington model in 1999. Both States have also participated in the CDC Pregnancy Risk Assessment Monitoring System and Behavioral Risk Factor Surveillance System since the 1990s. Study objectives were to describe the two Statewide FASD diagnostic networks; graphically compare the 4-Digit-Code FASD diagnoses and Prenatal Alcohol Exposure (PAE) over 2-3 decades and illustrate how network data helped guide FASD public health policies and track successful prevention efforts.

Methods: Retrospective descriptive study.

Results: FASD diagnostic outcomes were similar across 2,532 Washington and 2,469 Alaskan patients. PAE in each State followed similar annual trajectories from 1991-2020. Both States documented significant decreases in FAS and PAE in the 1990s. Clinic data helped guide public health policies.

Conclusions: Both States demonstrated the feasibility and value of establishing Statewide interdisciplinary FASD diagnostic clinical networks using the FASD 4-Digit-Code. Legislative support, centralized data collection, and use of a single, evidence-based FASD diagnostic system have been key to the long-term, ongoing success of these two diagnostic networks.

Keywords: Fetal alcohol spectrum disorder; FASD 4-Digit Diagnostic Code; Statewide interdisciplinary clinical networks; Prenatal alcohol exposure; PRAMS/BRFSS

Abbreviations: Alc: Alcohol; CNS: Central Nervous System; H: Height; SD: Standard Deviation; W: Weight; SDs: Standard Deviations; CDC: Center for Disease Control; FAS: Fetal Alcohol Syndrome; FASDPN: Fetal Alcohol Syndrome Diagnostic & Prevention Network; WA: Washington; AK: Alaska; PAE: Prenatal Alcohol Exposure; PRAMS: Pregnancy Risk Assessment Monitoring System; IEP: Individualized Education Program; SE: Static Encephalopathy; AE: Alcohol-Exposed; ND: Neurobehavioral Disorder; DHSS: Department of Health and Social Services; BRFSS: Behavioral Risk Factors Surveillance System; PFAS: Partial Fetal Alcohol Syndrome.

INTRODUCTION

Fetal Alcohol Spectrum Disorder (FASD) is a spectrum of physical and neurodevelopmental abnormalities caused by prenatal alcohol exposure [1]. Meaningful progress in FASD screening, diagnosis, intervention, surveillance, public health policy, research and ultimately prevention hinges on establishment of interdisciplinary FASD diagnostic clinics using a single evidence-based, comprehensive and reproducible

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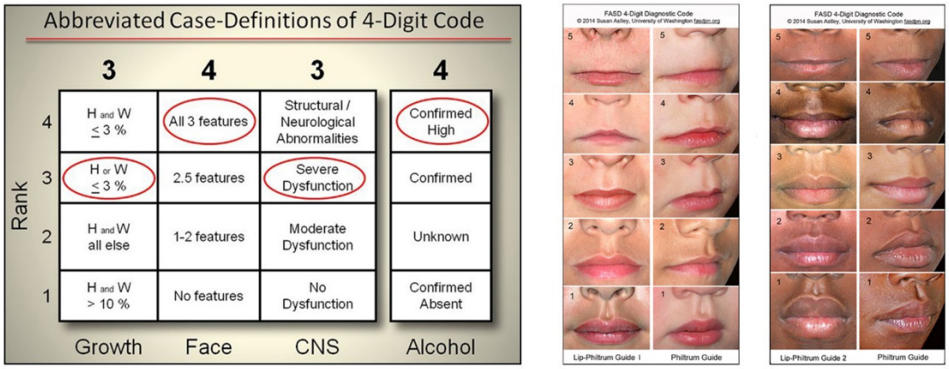
method of diagnosis [2-4]. In 1993, the University of Washington in Seattle Washington (WA) opened the first interdisciplinary FASD diagnostic clinic sponsored by the Center for Disease Control (CDC) as a FASD primary prevention study [2,3,5,6]. Data collected in the clinic was used to develop and validate the FASD 4-Digit Diagnostic Code in 1997 [4,7-9]. Creation of the diagnostic system paved the way for legislative expansion of the clinic through Senate Bill 5688 into a Statewide network of FASD diagnostic clinics, the WA Fetal Alcohol Syndrome Diagnostic & Prevention Network (FASDPN) [10,11]. The WA FASDPN is now in its 30th year of operation. This interdisciplinary Statewide FASD diagnostic system and model was adopted by Alaska (AK) in 1999 and continues to this date [12-14]. The WA interdisciplinary model and 4-Digit Code have been adopted worldwide. Over 1,700 clinicians from 35 countries have completed the FASD 4-Digit Diagnostic Code online course [15,16]. The primary objective of this study was to demonstrate the feasibility and value of establishing long term, Statewide interdisciplinary FASD diagnostic clinics using the FASD 4-Digit Diagnostic Code. To meet this objective:

1. The WA and AK Statewide FASD diagnostic network models are described.
2. The 4-Digit Code FASD diagnostic outcomes and CDC Pregnancy Risk Assessment Monitoring System [17-19] and CDC Behavioral Risk Factor Surveillance System [20,21] prenatal alcohol exposure histories documented over 2-3 decades are graphically summarized.
3. The impact data from these networks have had on helping: A) guide FASD public health policy and B) track successful prevention efforts is illustrated.

MATERIALS AND METHODS

Subjects

The diagnostic outcomes of all individuals (birth through adult) with confirmed prenatal alcohol exposure at any level, evaluated by the WA FASDPN from 1993-2021 (n=2,532) and the AK Department of Health and Social Services (now known as the Department of Health) FASD diagnostic teams from 1999-2021 (n=2,469) are graphically compared in this study. These diagnostic outcomes include 4-Digit Code Diagnostic Categories A-C, E-J as defined in Figure 1 and Table 1. All data was collected with Institutional Human Subjects approval.



4-Digit Code produces 4 Diagnostic Subgroups

Diagnosis		Growth	FAS Face	CNS		Alcohol
1. FAS	Fetal Alcohol Syndrome	growth	face	severe		alc
2. PFAS	Partial FAS		face	severe		alc
3. SE/AE	Static Encephalopathy / Alc Exposed			severe		alc
4. ND/AE	Neurobehavioral Disorder / Alc Exposed				moderate	alc

Figure 1: Abbreviated case-definitions of the FASD 4-digit code. The 4-digit code 3434 is one of 12 codes that fall under the diagnostic category Fetal Alcohol Spectrum (FAS). The 4-digit code produces four diagnostic subgroups broadly under the umbrella of Fetal Alcohol Spectrum Disorder (FASD): FAS (categories A, B), PFAS (category C), SE/AE (categories E-F), and ND/AE (Categories G-H) (Table 1). **Note:** Growth ranks are based on height and weight percentile. The 3 facial features of FAS are palpebral fissure lengths 2 or more Standard Deviation (SDs) below the mean, and a rank 4 or 5 smooth philtrum and thin upper lip using Lip-Philtrum quides 1 or 2. The Central Nervous System (CNS) scale reflects the probability of underlying CNS damage based on structural, neurological, and/or functional evidence. The higher the rank, the stronger the evidence or higher the probability that there is underlying CNS damage. CNS rank 1 (unlikely CNS damage) is selected when there is no evidence of dysfunction. CNS rank 2 (possible damage) is selected when there is moderate dysfunction (1 or 2 domains of brain function 2 or more SDs below the mean or multiple domains 1.5 SDs below the mean). Rank 3 (probable damage) is selected when there is severe dysfunction defined as 3 or more domains of brain function 2 or more SDs below the mean. Rank 4 (definite damage) is selected when structural/neurological abnormalities are present (microcephaly, abnormal Magnetic Resonance Imaging (MRI), etc.). Rank 4 alcohol reflects an exposure pattern consistent with the medical literature placing the fetus at "high risk" (generally high peak blood alcohol concentrations delivered at least weekly in early pregnancy). Rank 3 alcohol reflects a confirmed prenatal alcohol exposure at a level less than rank 4 or at a level that is unknown [7,8].

Table 1: 4-Digit diagnostic codes within each diagnostic category.

Category	Diagnostic name and codes
A	Fetal alcohol syndrome (alcohol exposed)
	2433 2434 2443 2444 3433 3434 3443 3444
	4433 4434 4443 4444
B	Fetal alcohol syndrome (alcohol exposure unknown)
	2432 2442 3432 3442 4432 4442
C	Partial fetal alcohol syndrome (alcohol exposed)
	1333 1334 1343 1344 1433 1434 1443 1444 2333 2334 2343 2344
	2333 2334 2343 2344 3333 3334 3343 3344 4333 4334 4343 4344
E	Sentinel physical finding(s)/static encephalopathy (alcohol exposed)
	3133 3134 3143 3144 3233 3234 3243 3244
	4133 4134 4143 4144 4233 4234 4243 4244
F	Static encephalopathy (alcohol exposed)
	1133 1134 1143 1144 1233 1234 1243 1244
	2133 2134 2143 2144 2233 2234 2243 2244
G	Sentinel physical finding(s)/neurobehavioral disorder (alcohol exposed)
	1323 1324 1423 1424 2323 2324 2423 2424 3123 3124 3223 3224
	3323 3324 3423 3424 4123 4124 4223 4224 4323 4324 4423 4424
H	Neurobehavioral disorder (alcohol exposed)
	1123 1124 1223 1224 2123 2124 2223 2224
I	Sentinel physical finding(s) (alcohol exposed)
	1313 1314 1413 1414 2313 2314 2413 2414 3113 3114 3213 3214
	3313 3314 3413 3414 4113 4114 4213 4214 4313 4314 4413 4414
J	No physical findings or CNS abnormalities detected (alcohol exposed)
	1113 1114 1213 1214 2113 2114 2213 2214

Note: CNS: Central Nervous System.

FASD 4-Digit Code

All subjects were diagnosed by interdisciplinary teams in WA and AK using a comprehensive, validated diagnostic system called the FASD 4-Digit Code, depicted in Figure 1 and Table 1 [7,8]. Briefly, the 4 digits of the FASD 4-Digit Code reflect the magnitude of expression of the 4 key diagnostic features of FASD, in the following order: 1. growth deficiency, 2. FAS facial phenotype, 3. CNS structural/functional abnormalities, and 4. Prenatal Alcohol Exposure (PAE). The magnitude of expression of each feature is ranked independently on a 4-point Likert scale, with 1 reflecting complete absence of the FASD feature and 4 reflecting a strong "classic" presence of the FASD feature. Each Likert rank is specifically case defined [7]. 4-Digit Codes range from 1111 to 4444. Each 4-digit diagnostic code falls into 1 of 22 unique clinical diagnostic categories (labeled A through V). Seven of the 22 diagnostic categories (4-Digit Categories A-C and E-H) fall broadly under the umbrella of FASD (A: FAS/ alcohol exposed; B: FAS/alcohol exposure unknown; C: Partial FAS/alcohol exposed; E&F: Static encephalopathy/ alcohol exposed, and G&H: Neurobehavioral disorder/alcohol exposed). Diagnostic categories I and J are also included in this study for they reflect the subset of patients with confirmed PAE that present only with growth deficiency and/or the FAS facial features (I: Sentinel physical findings/alcohol-exposed) or present with normal outcomes (J: No sentinel physical findings or CNS abnormalities/alcohol-exposed). Categories I and J are not considered under the umbrella of FASD in accordance with the FASD 4-Digit Code.

Prenatal alcohol exposure

Measures of prenatal alcohol exposure were obtained from three sources. The first source was each patient's 4-Digit Code prenatal alcohol exposure 4-point Rank documented at the time of their FASD diagnostic evaluation (Figure 1, Table 1) [7,8]. Alcohol exposure histories reported to the clinics typically come from the birth mother, other family members and/or past medical and social service records. The second and third sources of PAE were obtained from two national CDC surveillance systems, the Pregnancy Risk Assessment Monitoring System (PRAMS) and Behavioral Risk Factors Surveillance System (BRFSS) [17 - 21]. The PRAMS and BRFSS surveillance systems document the annual prevalence of alcohol use during pregnancy across representative samples of each State's general population. Over the decades, some of the questions on the PRAMS and BRFSS

surveys changed preventing one from tracking the same alcohol metric across the entire time period 1991-2015. In addition, not all States chose to include the same alcohol metrics in their annual surveys. PRAMS and BRFSS PAE metrics that were available from both States over the same period of years are presented in this study.

Analyses

Descriptive analyses (proportions) were used to graphically summarize the sociodemographics, FASD diagnostic outcomes and reported prenatal alcohol exposures for each State. It was not the intent of this study to hypothesize and empirically assess how exposures and FASD outcomes may differ between the two States or change over time. The FASD diagnostic outcomes are derived from clinical populations that are typically not representative of the general population. For example, hypothetically, if the prevalence of FAS was higher in the WA clinical population than the AK clinical population, that would not necessarily mean WA had a higher prevalence of FAS in its general population. There are many factors that influence which individuals request and receive an FASD diagnosis (access to diagnostic services, knowledge of prenatal alcohol exposure, caregiver willingness to participate in a FASD diagnostic evaluation, medical insurance coverage, etc.). One factor that is not influencing potential contrasts between the WA and AK FASD outcomes is their use of a single FASD diagnostic system, the FASD 4-Digit Code. In contrast to the FASD diagnostic outcomes, the prenatal alcohol exposure data generated by the CDC PRAMS and BRFSS surveillance programs are designed to be representative of each State's general population. The purpose of including these measures of PAE was to provide a context or background from which to qualitatively interpret the WA and AK FASD outcomes, visually compare the drinking patterns between the two States and allow Readers to compare the drinking patterns documented in WA and AK to other States participating in PRAMS and/or BRFSS. Empirically contrasting the WA and AK PRAMS and BRFSS prenatal alcohol exposure patterns would warrant a separate study.

RESULTS

Objective 1: Establishment and description of the WA and AK Statewide FASD diagnostic clinical networks

Washington state: The term FAS was first coined in WA State at the University of Washington in 1973 [22,23]. Over the next 50 years, WA State engaged in an extensive, multifaceted effort to screen, diagnose, treat, track and ultimately prevent FASD. A comprehensive history of these efforts is posted on the WA State FASD website [24]. Although diagnostic services in WA commenced as early as 1973, diagnosis was typically conducted by a geneticist or dysmorphologist relying largely on clinical impression of physical features. In 1993, the University of Washington opened the first interdisciplinary FASD diagnostic clinic sponsored by the CDC as a FASD primary prevention study [2,3,5]. In 1995, the WA Legislature through Senate Bill 5688 expanded the clinic into a Statewide network of FASD diagnostic clinics (Figure 2) led by the core clinical/research/training clinic at the University of Washington in Seattle, WA [11]. Susan J. (Astley) Hemingway, Ph.D., Professor of Epidemiology/Pediatrics, directs the FASDPN. All WA FASDPN clinics use an interdisciplinary approach to diagnosis guided by the FASD 4-Digit Diagnostic Code and submit data to the core clinic at the University of Washington with patient consent and human subject's approval. The interdisciplinary team includes a medical doctor, psychologist, speech language pathologist, occupational therapist, social worker, family advocate and public health professional. All team members complete the FASD 4-Digit Code Online Course [15]. Individuals across the lifespan with a confirmed prenatal alcohol exposure at any level or the full Rank 4 FAS facial phenotype are eligible for an evaluation. A FASD diagnostic evaluation is conducted in a single 4-hour evaluation. In preparation for the evaluation, all birth, medical, school, and social service records are collected on the patient. These records provide important data (growth, medical, neuropsychological test scores, other adverse prenatal/postnatal exposures) that are critical to deriving an accurate FASD diagnosis. On the day of the evaluation, the caregivers participate in a joint interview with the medical doctor and social worker while the patient is assessed by the psychologist, speech-language pathologist and occupational therapist. Standardized neuropsychological assessments are administered to assess all aspects of brain function (cognition, executive function, memory, language, attention, adaptation, motor, sensory, etc.). Height, weight, head circumference and facial features are also measured. The team uses data collected in the clinic as well as the data from past records to derive the FASD 4-Digit Code. They also compose a comprehensive intervention plan addressing medical, behavioral, educational, placement and safety issues. The team shares the diagnosis and intervention plan with the family and submits an 8 to 10-page comprehensive medical summary to the patient's medical record. All phases of data collection and report generation are documented on standardized, electronic templates available on the FASDPN website [25]. The team conducts two diagnostic evaluations per clinic, one in the morning and one in the afternoon. Twenty years of patient surveys confirmed the FASDPN interdisciplinary diagnosis model using the 4-Digit Code affords patients and their families substantial access to interventions that meet their needs across the spectrum of FASD diagnoses [26]. The mission of the FASDPN is prevention of FASD through diagnosis, intervention, screening, surveillance, training, public health policy and research. The WA State FASDPN, now in its 30th year, has achieved each of these missions [27]. The FASDPN has diagnosed over 3,000 patients with PAE across the lifespan. It has also established one of the world's largest clinical/research databases with patient consent, leading to over 100 peer-reviewed publications [28,29]. The WA FASDPN has expanded both nationally and internationally through the training of over 1,700 clinicians in 35 countries. The FASDPN has provided FASD training to over 10,000 WA State community professionals over the 30 years with particular focus on student professionals commencing their careers in public service [30].

Alaska State: Since 1999, the Alaska Department of Health and Social Services (DHSS), now the Alaska Department of Health, has coordinated and funded a Statewide network of community-based FASD diagnostic teams [12]. The number and location of FASD diagnostic teams around the State has varied over time as shown in Figure 2. Originally, 17 teams were trained to serve across the State. In 2023, there are three teams. Diagnosis of FASD is conducted by these interdisciplinary teams using the FASD 4-digit diagnostic code [7]. Team members are trained by completing the FASD 4-Digit code online course [15]. Ideally within this model, an interdisciplinary team of

clinicians (i.e., medical provider, psychologist, speech language pathologist, occupational therapist, and family advocate) is required to diagnose FASD because the damage caused by prenatal alcohol exposure impacts all aspects of an individual's growth and brain development. Challenges with maintaining all these professionals on a team, especially in rural settings, have required flexibility in functioning [12]. In the event a psychologist, speech language pathologist, or occupational therapist is not available, teams have been allowed to use testing and assessment information from professionals with similar assessment skills and from service entities that may be involved with the individual (e.g., school Individualized Education Program (IEP) documents, other private practice professionals' reports, etc.). The expertise of a medical provider is required to assess and interpret the physical and neurological components of the disorder (i.e., growth deficits, facial anomalies, seizure disorders). The expertise of a psychologist, speech language pathologist, and occupational therapist is required to assess the CNS functional component of the disorder as described above. Team members are trained by completing the FASD 4-digit code online course [15]. Over the past 20 years, there have been an estimated 3,000 to 4,000 individuals evaluated by the FASD diagnostic teams; assessment data for about 3,000 of these individuals were reported to the State of Alaska [12].

Objective 2: WA and AK FASD outcomes and prenatal alcohol exposures

Sociodemographics: The distribution of patient age at diagnosis, type of caregiver at diagnosis, sex at birth and race are compared between the 2,469 individuals evaluated in Alaska and the 2,532 individuals evaluated in WA as shown in Figure 3. AK and WA evaluated individuals across the lifespan with the majority between 6.0 and 12.9 years of age. WA evaluated a higher proportion (14.9%) of infant/toddlers (birth to 2.9 years of age) than AK (4.2%). Both States evaluated a comparably higher proportion of males than females. The racial distribution of the patient populations cannot be meaningfully compared between the two States because 53.7% of the patients from Alaska did not have race recorded. Whites appeared to be underrepresented (47.8%) in the clinical population evaluated in the WA FASDPN clinics when compared to the 2020 census for WA (7.7 million total population: White (alone) 77%, American Indian/Alaska Native (alone) 2%, Black (alone) 5%, other (alone) and mixed race 16%). For reference, the 2020 census for AK was as follows: (0.7 million total population: White (alone) 65%, American Indian/Alaska Native (alone) 16%, Black (alone) 4%, other (alone) and mixed race 15%). The majority of patients evaluated in both States were in out-of-home care at the time of diagnosis with only 10.3% and 17.2% still in the care of their birth mother in AK and WA respectively [31].

Figure 2: Geographic distribution of FASD diagnostic services in Washington (WA) and Alaska (AK): Location of Fetal Alcohol Spectrum Disorder (FASD) diagnostic clinics in WA over 30 years. Number of assessments by Behavioral Health Region in AK since 1999 [12].

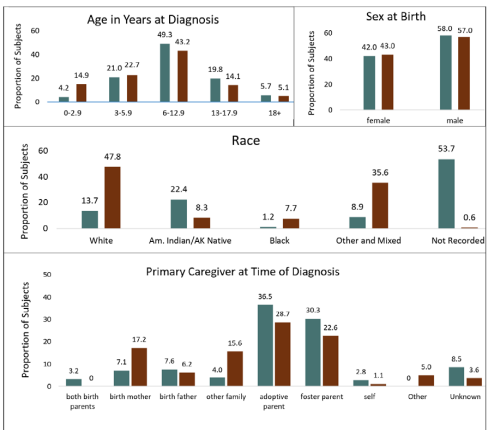


Figure 3: Sociodemographic profiles of the Alaska (AK) and Washington (WA) Fetal Alcohol Spectrum Disorder (FASD) clinical populations: The race categories represent White (alone), American Indian/Alaska Native (alone), Black (alone), other race (alone) which includes Asian, Native Hawaiians and other Pacific Islanders, mixed (2 or more races). Over 95% of the "other and mixed" race category is mixed race. **Note:** ( ) Alaska (n=2,469), ( ) Washington (n=2,532).

Growth, Face, CNS and Alcohol Ranks: The distribution of the 4-digit code ranks for growth, face, CNS and prenatal alcohol exposure for the AK and WA clinical populations are presented in Figure 4. The proportion of patients presenting with moderate and high PAE (ranks 3,4) was near identical between the two States. Roughly 20-30 percent of the AK and WA patients presented with mild to severe growth deficiency (height and/or weight at or below the 10th percentile). The moderate to severe expression of the FAS facial phenotype (ranks 3, 4) was observed in 14 to 30 percent of the two clinical populations. The WA clinical population was more likely to present with moderate CNS dysfunction (52.2% CNS rank 2) than severe CNS dysfunction (22.7% CNS rank 3). In contrast, the AK clinical population was more likely to present with severe CNS dysfunction (47.5% CNS rank 3) than moderate CNS dysfunction (32.5% CNS rank 2). This is explained in part by the higher proportion of infant/toddlers (birth to 3 years of age) attending the WA clinics (14.9%) relative to the AK clinics (4.2%). Infants/toddlers are less likely to meet criteria for severe CNS dysfunction because they are too young to assess higher order brain functions like memory, executive function and language that have not yet fully matured. Severe CNS dysfunction (rank 3) requires 3 or more domains of dysfunction 2 or more SDs below the mean. Moderate CNS dysfunction (rank 2) requires only 1 or 2 domains of dysfunction 2 or more SDs below the mean or multiple domains 1.5 SDs below the mean.

Prenatal alcohol exposure: The annual prevalence of alcohol use during pregnancy appeared fairly comparable between AK and WA over the decades based on data from two Statewide CDC surveillance systems Pregnancy Risk Assessment Monitoring System and Behavioral Risk Factors Surveillance Systems and the 4-Digit Code prenatal alcohol exposure Rank based on records available at the time of the FASD diagnostic evaluations (Figure 4 and 5) [7,8,17-21]. The PRAMS and BRFSS Statewide surveillance systems strive to document alcohol use during pregnancy across representative samples of the general population. The prevalence of any level of alcohol use during pregnancy reported annually to PRAMS by both States decreased from 1993-1998 (Figure 5A). This decrease is discussed in more detail below under objective 3B. The decrease in both States coincided with the establishment of the WA and AK FASD diagnostic and prevention programs that included substantial Statewide efforts to educate the public about the risks of drinking during pregnancy [12,27]. By 1994, both States met or exceeded the healthy people 2000 goal of no more than 10% of women drinking during pregnancy. AK went on to meet the health people 2010 goal of no more than 6% of women drinking during pregnancy from 2000-2010 [32]. WA experienced an increase in drinking from 2000-2010 but remained below the healthy people 2000 goal of 10%. Neither State met the healthy people 2020 goal of 1.7% by 2015. In 2016, the CDC PRAMS survey was revised to document heavy drinking (>8 drinks per week) three months prior to pregnancy, a metric that likely reflects prenatal alcohol exposure before a woman knows she is pregnant (Figure 5B). The prevalence of heavy drinking (>8 drinks per week) three months prior to pregnancy between 2016 and 2020 was comparably stable (2% to 4%) between the two States as documented by PRAMS [17]. The proportion of pregnant women reporting any level of drinking between 2005 and 2021 was higher in WA than AK and closely reflected outcomes documented by PRAMS in the same time period (Figure 5C). The proportion of pregnant women reporting binge drinking (>=4 drinks per occasion) appeared to increase from 1% to 5% between 2006 and 2021 in both States (Figure 5D) [20]. Once again, the data collected by PRAMS and BRFSS appeared roughly comparable across the years. The CDC healthy people 2020 target for pregnant women abstaining from binge drinking in the past 30 days was 100%. Comparable levels of prenatal alcohol exposure were also observed between the WA and AK FASD diagnostic clinic populations. Fifty-one percent of all patients evaluated in each State's FASD diagnostic clinics had documented high prenatal alcohol exposure (4-Digit Code rank 4) (Figure 4). When these patients were sorted by the year they were born (1991 through 2015), the proportion with high rank 4 exposure within each birth cohort was comparable between both States, fluctuating between 45% to 55%. (Figure 5E).

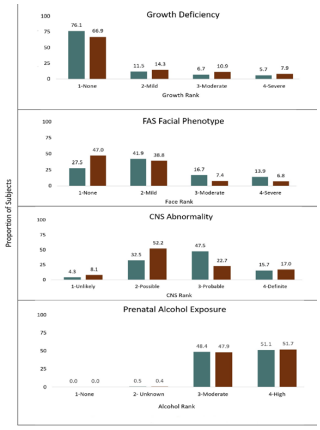


Figure 4: Distribution of growth, face, brain and alcohol ranks for Alaska (AK) and Washington (WA): Distribution of the 4-digit code ranks for growth, face, Central Nervous System (CNS) and prenatal alcohol exposure are compared between the 2,469 individuals diagnosed in Alaska and the 2,532 individuals diagnosed in WA. **Note:** ( ) Alaska, ( ) Washington.

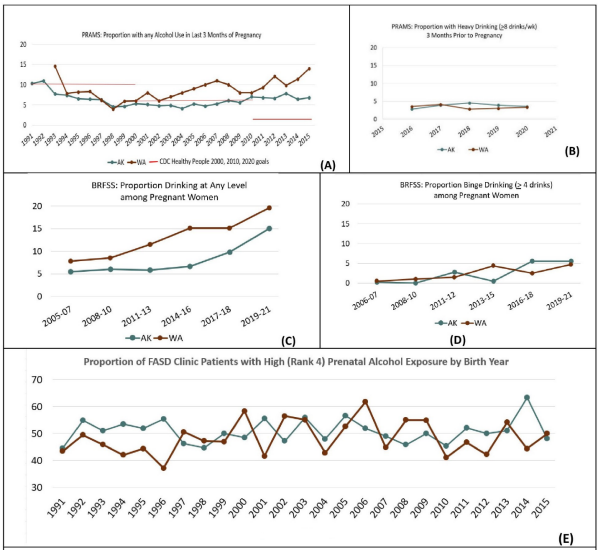


Figure 5: Prevalence of reported maternal drinking during pregnancy in Alaska (AK) and Washington (WA): Proportion of pregnancies in AK and WA with A, B, C, D, E. **Note:** ( ) AK, ( ) WK; (A) any level of alcohol use in the last 3 months of pregnancy, (B) heavy drinking (>=8 drinks per week) 3 months prior to pregnancy, (C) Any level of drinking while pregnant, (D) binge level drinking (>=4 drinks/occasion) while pregnant, (E) Proportion of patients evaluated in the WA and AK clinics with high (4-Digit Code Rank 4) prenatal alcohol exposure sorted by birth cohort. Red lines reflect Center for Disease Control (CDC) Healthy People 2000 (10%), 2010 (6%), and 2020 (1.7%) goals for the proportion of pregnant women reporting alcohol use. Over the decades, the Pregnancy Risk Assessment Monitoring System (PRAMS) and Behavioral Risk Factors Surveillance System (BRFSS) questionnaires have been updated/revised, thus comparable fields of data are not always available across all years [18,19,21,32,50,51].

FASD diagnostic outcomes by age: FASD diagnostic outcomes by age group for WA and AK are presented in Figure 6. The proportion of patients with FAS appears comparable between WA and AK and comparable between each age group ranging from 2.0% to 8.3%. AK documented a higher proportion of PFAS (15% to 24%) across all age groups relative to WA (4% to 6%). Both States documented a higher proportion of ND/AE than SE/AE among young patients and a higher proportion of SE/AE than ND/AE among older patients. This would be expected since patients under 8-9 years of age are too young to assess higher order brain functions like memory, executive function and language that have not yet fully matured. A diagnosis of Static Encephalopathy/Alcohol-Exposed (SE/AE) requires standardized psychometric evidence of three or more domains of brain function, 2 or more Standard Deviations (SDs) below the mean. In contrast, a diagnosis of Neurobehavioral Disorder/Alcohol-Exposed (ND/AE) requires 1 to 2 domains of brain function 2 SDs below the mean or multiple domains 1.5 SDs below the mean.

FASD diagnostic outcomes by race: FASD diagnostic outcomes by race for WA and AK are presented in Figure 7. The prevalence of FASD diagnostic outcomes appeared largely comparable across the different races within each State.

Distribution of FASD diagnoses by year: The distribution of FASD diagnoses by year for WA and AK are presented in Figure 8. The distribution of FASD diagnoses remained relatively similar from year to year within each State despite the fact that the number of FASD clinics varied annually as did the clinicians providing the diagnostic services. AK observed a higher prevalence of PFAS and lower prevalence of ND/AE than WA. The cumulative proportion of patients with the most severe outcomes (FAS, PFAS and SE/AE) hovered around 60% annually in AK compared to 40% annually in WA.

Objective 3A: Guiding public health policy and legislation to support individuals with FASD

Data collected by the WA FASDPN was instrumental in helping guide public health policies to better meet the needs of individuals with FASD and their families. AK also implemented numerous public health policies over the decades that together, with the establishment of their FASD diagnostic clinics, helped meet the needs of individuals impacted by FASD. Below are a few examples of these policies and legislation. More comprehensive summaries are available from, the Alaska Mental Health Trust Authority and the Alaskan UAA College of Health [12,13,27].

Washington State:

- 1997: Expansion of the CDC-sponsored University of Washington FASD interdisciplinary diagnostic clinic into the Statewide network of clinics (FASDPN) through Substitute Senate Bill 5688 [11]. The WA FASDPN has been funded by the WA State Legislature for 30 consecutive years. The Senate Bill also established the WA FASD Interagency Workgroup ensuring coordination of FASD programs across the Department of Social & Health Services, Superintendent of Public Instruction, Department of Corrections and Department of Health. Senate Bill 5688 required the core clinic at the University

of Washington to collect data from all FASDPN network clinics and share an annual report with the above-named State departments summarizing the demand for diagnostic services, the ability to meet the demand and the PAE and FASD profiles of the patients served. These outcomes are also shared in aggregate, open-access form via our Tableau interactive dashboards [28].

- 1997-2009: Establishment of a Statewide evidence-based FASD prevention program (Parent-Child Assistance Program), evidence-based FASD intervention program (Families Moving Forward) and caregiver advocacy program (FASD Focus NW) [33-35].
- 2001: WA State law requiring warning signs from the Liquor Control Board at all points-of-purchase for alcohol warning against the possible danger of birth defects which may be caused by consumption of alcohol during pregnancy Washington Administrative Code 314-11-060 [36].
- 2014: Comprehensive report to the WA State Legislature on achievements, current challenges and recommended solutions to screen, diagnose, treat and prevent FASD [27].
- 2015: Acceptance of FASD as a qualifying condition for developmental disability assistance [37].
- 2022: Elimination of the use of IQ scores when determining eligibility for developmental disability assistance. WA Second Substitute House Bill 2008 [38].
- 2023: An act relating to expanding prevention services, diagnoses, treatment, and support for prenatal substance exposure including prenatal alcohol exposure. WA Second Substitute House Bill 1168 [39].

Alaska State:

- 1999: Alaska Senator Ted Stevens, Chairman of the Senate Appropriations Committee added $29 million into the federal budget to target FASD in Alaska for five years. A massive diagnostic effort began in 2000. The State created FASD diagnostic teams- from Sitka to Barrow, Fairbanks to Bethel to diagnose children with FASD. Seventeen were funded [14].
- 2001: Alaska Statute requiring bars, liquor stores and restaurants to display 11-by-14-inch signs that drinking while pregnant can lead to birth defects [40].
- 2012: The Alaska State Legislature though Senate Bill 151 made an FASD diagnosis a mitigating circumstance to be considered in sentencing for felony level criminal offenses through [41].
- 2012: The Alaska State Legislature permanently recognized September 9 as FASD Awareness Day in Alaska through Senate Bill 127. September 9 is recognized worldwide as FASD Awareness Day [42].
- 2018: Alaska FASD Strategic Plan 2017-2022. Governor's Council on Disabilities and Special Education (January 29, 2018). Included in the report is a detailed history of FASD efforts in Alaska from the 1970s through 2022 [14].
- 2020: Alaska FASD Diagnostic Team Data Analysis, Policy and Prevention Recommendations prepared for the Alaska Mental Health Trust Authority [12].

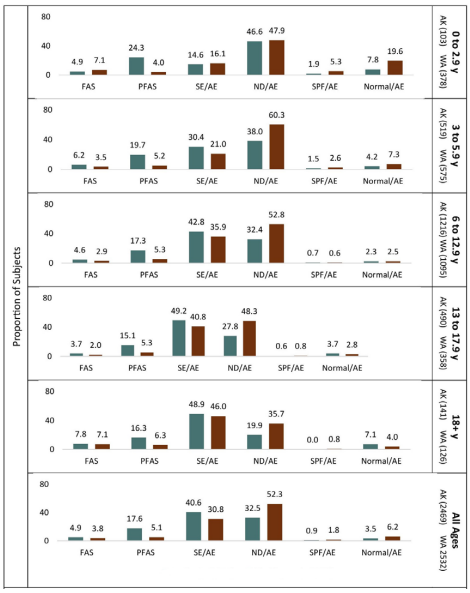


Figure 6: Alaska (AK) and Washington (WA) Fetal Alcohol Spectrum Disorder (FASD) diagnostic profiles by age group. The proportion of patients with Fetal Alcohol Spectrum (FAS) appears clinically comparable between AK and WA across all age groups. **Note:** (■) Alaska (n=2,469), (■) Washington (n=2,532). AK documented a higher proportion of PFAS (15% to 24%) across all age groups relative to WA (4% to 6%). Both States documented a higher proportion of Neurobehavioral Disorder (ND)/ Alcohol-Exposed (AE) than Static Encephalopathy /Alcohol-Exposed (SE)/AE among young patients and a higher proportion of SE/AE than ND/AE among older patients. This would be exp ected since patients under 8 years of age are too young to assess higher order brain functions like memory, executive function and language that have not yet matured.

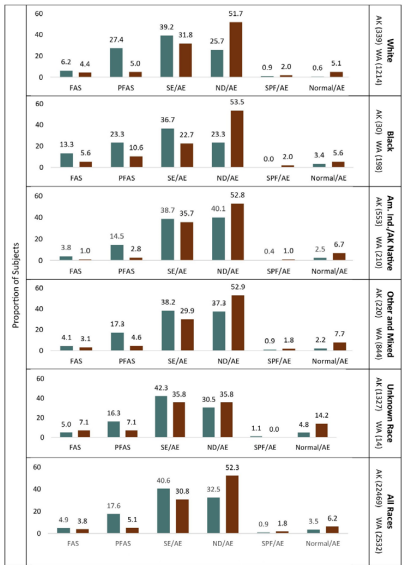


Figure 7: Alaska (AK) and Washington (WA) Fetal Alcohol Spectrum Disorder (FASD) diagnostic outcomes by race. The prevalence of FASD diagnostic outcomes appears comparable across all races within each State. **Note:** ( ) Alaska (n=2,469), ( ) Washington (n=2,532).

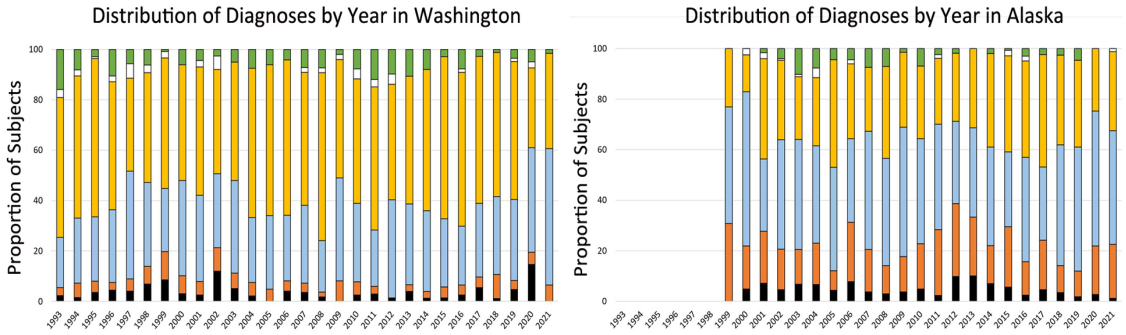


Figure 8: Distribution of Fetal Alcohol Spectrum Disorder (FASD) diagnoses by year of diagnosis in Washington and Alaska. The distribution of Fetal Alcohol Spectrum Disorder (FASD) diagnoses remained relatively similar from year to year within each State despite the fact the number of FASD clinics varied annually over the decades as did the clinicians providing the diagnostic services. Washington (n=2,532); Alaska (n=2,469). **Note:** ( ) Fetal Alcohol Spectrum (FAS), ( ) Partial Fetal Alcohol Spectrum (PFAS), ( ) Static Encephalopathy (SE)/ Alcohol-Exposed (AE), ( ) Neurobehavioral Disorder (ND)/AE), ( ) Sentinel Findings ( ) Normal/AE.

Objective 3B: Tracking successful prevention efforts

Washington State: To assess the effectiveness of fetal alcohol syndrome prevention efforts, one must be able to estimate accurately the prevalence of fetal alcohol syndrome over time in population-based samples. With the establishment of the WA FASDPN clinics, the development of the FAS Facial Photographic Analysis Software, the creation of the FASD 4-Digit Diagnostic Code, the establishment of the Foster Care Fetal Alcohol Syndrome Screening Program, and the collection of PRAMS data on maternal use of alcohol during pregnancy, the tools, methods and infrastructure for assessing the effectiveness of fetal alcohol syndrome primary prevention efforts in Washington State were in place [7,17-19,43,44]. A cross-sectional study was conducted in 2004 to determine whether the prevalence of fetal alcohol syndrome among children in a foster care population, born between 1993 and 1998, decreased with the documented decrease in prevalence of maternal use of

alcohol during pregnancy from 1993 and 1998 in Washington State documented through PRAMS [45]. The prevalence of maternal drinking during pregnancy in Washington State declined significantly ($p<0.001$) from 1993 to 1998 as did the prevalence of fetal alcohol syndrome among foster children born 1993-98 ($p<0.03$). These observations support the likelihood that FAS prevention efforts in Washington State were working successfully. Fundamental to WA State's success in creating and implementing FASD screening, diagnostic, intervention and prevention tools and programs over the decades is the ongoing support received from the State Legislature. In April 2023, the Governor of WA signed House Bill 1168, an act relating to providing prevention services, diagnoses, treatment and support for prenatal substance exposure [39]. This bill compliments and expands Senate Bill 5688, enacted in 1995 supporting efforts directed at the early identification of and intervention into the problems associated with fetal alcohol exposure through the creation of the Fetal Alcohol Syndrome Diagnostic and Prevention Network [11].

Alaska State: In a 2009 CDC-sponsored study, medical record abstractions were completed for all potential FAS cases reported to the Alaska Birth Defects Registry for children who were at least 6 years of age (birth years 1996-2002) [46]. Data from these abstractions was linked to birth certificates to determine FAS prevalence estimates. From 1996 to 2002, Alaska experienced a 32% decrease in FAS birth prevalence from 19.9 to 13.5 per 10,000 live births ($p=0.05$). Decline in the overall FAS prevalence was limited entirely to Alaska Native children who experienced a 49% decline from 63.1 to 32.4 per 10,000 live births ($p=0.003$). The prevalence among non-Native children increased 64% from 3.7 to 6.1 per 10,000 live births ($p=0.18$). The observed decline occurred in association with several prevention activities: development and sustainability of a network of community-based FASD Diagnostic Teams; development of university-level FASD curricula and Statewide training programs for educators and providers; a Statewide multi-media public awareness campaign; and increased substance use screening in primary care settings. The temporal association of declining FAS prevalence with prevention activities suggests that the interventions played a role.

DISCUSSION

WA and AK have demonstrated the feasibility of implementing the 4-Digit Code and the value of establishing longstanding, Statewide, interdisciplinary FASD diagnostic clinical networks. FASD diagnostic clinics and the databases derived from them serve as the foundation for FASD screening, diagnosis, intervention, training, research, public health policy and prevention [2,3,7-9,12,13,15,16,26-28,30,34,37,39,44-46,48,49,52-54]. Ongoing legislative support, centralized data collection, and use of an evidence-based FASD diagnostic system with online training continue to be key to the ongoing success of these two networks [7,15]. Interdisciplinary FASD diagnostic clinics using the 4-Digit Code have been established worldwide. Their FASD diagnostic profiles are compared and contrasted on our Tableau interactive dashboards [28]. Although AK and WA have maintained Statewide FASD diagnostic clinics for 20-30 years respectively, establishing and maintaining interdisciplinary FASD diagnostic teams are not without challenges. Briefly, challenges include geographic reach, training and turnover of professionals on FASD diagnostic teams, stigma related to those who consume alcohol during pregnancy and their offspring, funding, and community education/readiness. Utilizing telemedicine platforms like zoom proved indispensable during the COVID pandemic for remotely connecting clinicians and patients with the core interdisciplinary teams when in-person attendance was not possible. These platforms continue to be useful to address some of the challenges faced in rural communities. Having access to self-paced online diagnostic training programs like the FASD 4-Digit Code Online Course greatly facilitated training of new clinical team members [15].

To enhance interest and education related to FASD the University of Alaska College of Health in Anchorage established a 3-credit elective asynchronous course in 2021 for allied health and related professional students entitled Interdisciplinary Approaches to Fetal Alcohol Spectrum Disorders (FASD): Best Practices in Alaska [49]. For comprehensive reviews of WA and AK FASD diagnostic and prevention efforts, challenges, accomplishments and programmatic recommendations, please see the 2014 comprehensive report to the WA State Legislature on achievements, current challenges and recommended solutions to screen, diagnose, treat and prevent FASD prepared by the WA FASD Interagency Work Group , the 2020 Alaska FASD Diagnostic Team Data Analysis, Policy & Prevention Recommendations and the 2021 Alaska FASD Data Systems Development: Gaps, Opportunities & Recommendations prepared for the Alaska Mental Health Trust Authority [12,13,27].

CONCLUSION

WA and AK have demonstrated the feasibility and value of establishing statewide interdisciplinary FASD diagnostic clinical networks using the FASD 4-Digit-Code. Legislative support, centralized data collection, and use of a single, evidence-based FASD diagnostic system with online training have been key to the long-term, ongoing success of these two diagnostic networks. FASD diagnostic outcomes were similar across the 2,469 Alaskan and 2,532 Washington patients diagnosed over 20 and 30 years respectively. Alcohol use reported by pregnant women in WA and AK, as documented by the CDC PRAMS and BRFSS population-based surveillance systems, followed similar annual trajectories from 1991-2020.

Primary prevention of FASD remains the ultimate goal. To assess the effectiveness of FAS prevention efforts, one must be able to accurately estimate the prevalence of FAS over time in population-based samples. With the establishment of the WA FASDPN clinics, the development of the FAS Facial Photographic Analysis Software, the creation of the FASD 4-Digit Diagnostic Code, the establishment of the Foster Care Fetal Alcohol Syndrome Screening Program and the collection of PRAMS data on maternal use of alcohol during pregnancy, the tools, methods and infrastructure for assessing the effectiveness of FAS primary prevention efforts in Washington State were in place [7,17-19,27,33,43,44]. As early as the 19 90s, WA documented significant decreases in the prevalence of FAS and PAE. AK also documented a significant decline in the birth prevalence of FAS in the 1990s using medical record review of all cases reported to the Alaska Birth Defects Registry. The decline in FAS occurred in association with the establishment of their FASD diagnostic clinics, statewide training of educators and clinicians and public awareness campaigns.

Establishing and maintaining FASD diagnostic and prevention networks are not without challenges. The benefits to families impacted by FASD, however, far outweigh the challenges.

ACKNOWLEDGEMENTS

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RESEARCH REPORT

Comparing narrative storytelling ability in individuals with autism and fetal alcohol spectrum disorders

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Abstract

Background: Narrative discourse, or storytelling, is used in daily conversation and requires higher-level language and social communication skills that are not always captured by standardised assessments of language. Many autistic individuals and individuals with fetal alcohol spectrum disorders (FASD) have difficulties with both social communication and language skills, and narrative discourse analysis offers an ecologically relevant approach to assessing those challenges.

Aims: This study investigated narrative discourse in individuals with autism and FASD, as well as an age- and sex-matched comparison group.

Methods and Procedures: Narratives from 45 adolescents and adults, 11 with autism, 11 with FASD and 23 age- and sex-matched comparison participants were elicited using a wordless storybook. They were then transcribed orthographically, formatted to the Systematic Analyses of Language Transcript (SALT) convention and scored based on the SALT Narrative Scoring Scheme (NSS), a standardised language analysis protocol. In addition to the NSS total score, which assesses the overall structure and cohesion of the narratives produced, local and global measures of language ability were also employed. The local language measures included the number of mental state and temporal relation terms produced, while the global language measures included mean length of utterance, total different words, total words, total utterances, rate of speech, the number of mazes (e.g., repetitions, 'um', 'uh' or self-corrections) per total word and the NSS total score.

Outcomes and Results: Using the SALT *Language Sample Analysis* tool, our results revealed that on global language measures, group differences were found on rate of speech, number of mazes per total words and the description of conflict/resolution in the narratives produced. The autism group produced significantly more mazes per total word and scored higher on the NSS conflict/resolution category score compared to the FASD and comparison groups. Both the autism and FASD groups spoke at a lower rate than the comparison group. On local language measures of narrative production, all groups were comparable, on average.

Conclusions and Implications: While many aspects of narrative discourse in the autism and FASD groups were similar to each other and to the comparison group, we observed group differences on global measures of narrative production and significant individual variability within groups, suggesting that narrative abilities considered at an individual level may provide important clinical information for intervention planning. Future research should also consider additional variables that influence narrative discourse, such as motivation, distractibility or decision-making of individual participants.

KEYWORDS
autism, FASD, language ability, narrative ability, narrative storytelling

What this paper adds

What is already known on the subject

- Narrative discourse, or storytelling, is used in daily conversational interactions and reveals higher-level language skills that may not be well captured by standardised assessments of language. Many autistic individuals and individuals with fetal alcohol spectrum disorders (FASD) show difficulty with pragmatic and expressive language skills.

What this paper adds to existing knowledge

- We found that many aspects of the narratives produced by the adolescents/young adults in the autism and FASD groups were comparable to each other and to the neurotypical group. However, the groups differed on three global measures of narrative production: rate of speech, number of mazes per total words and the description of conflict/resolution in the narratives produced. Also, significant variability was observed within groups, suggesting that narrative abilities should be considered at an individual level as opposed to their clinical groups.

What are the potential or actual clinical implications of this work?

- This study showed that narrative discourse is an appropriate task that can be added to routine clinical assessments of language abilities in autistic adolescents/young adults as well as those with FASD or typical development and has the potential to reveal higher-level, real-world language skills. An important clinical implication of this study is that narrative language abilities should be considered at an individual level and individual-tailored interventions based on ability level due to the variability observed across individuals.

INTRODUCTION

Narrative discourse, or storytelling, is a form of communication aimed at constructing a shared experience between the storyteller and listeners. As such, it is important for making social-emotional connections with others, for sharing personal perspectives and interests, and for building a common ground of shared knowledge in a

social network. Successfully constructing these shared experiences requires speakers to have adequate language and social communication skills. As a result, narrative discourse is often challenging for neurodiverse individuals who have impairment in social communication and language, such as those with autism (e.g., Barnes & Baron-Cohen, 2012; Colle et al., 2008; Losh & Gordon, 2014) and fetal alcohol spectrum disorders (FASD; Coggins et al., 2007; Ganthous et al., 2017).

Autism is characterised by persistent deficits in social communication functioning accompanied by restricted, repetitive patterns of behaviour, interests or activities (American Psychiatric Association, 2013) and language impairment affects up to 63% of autistic individuals (Levy et al., 2010). It is estimated that 1 in 100 people around the world are diagnosed with autism with variability across sociodemographic groups (Zeidan et al., 2022). In the United States, the prevalence is estimated to be 1 in 36 children (Maenner et al., 2023).

Fetal Alcohol Syndrome (FAS) is a permanent birth defect caused by exposure to the teratogen ethyl alcohol during pregnancy. FAS is characterised by significant central nervous system (CNS) abnormalities, growth deficiency and a unique cluster of three minor facial anomalies—small eyes, thin upper lip and a flat philtrum (Astley, 2004). Most children impaired by prenatal alcohol exposure will not receive a diagnosis of FAS (Astley, 2010) and will instead receive a diagnosis of one of a variety of FASD diagnoses with FAS representing the most severe end of this spectrum. If the degree of CNS dysfunction is used to characterise FASD diagnoses, the term 'Static Encephalopathy, Alcohol Exposed (SE/AE)',—can be used to indicate a significant CNS dysfunction in the context of prenatal alcohol exposure, and the term 'Neurobehavioural Disorder, Alcohol Exposed (NB/AE)'—to indicate a mild-to-moderate CNS dysfunction in the context of prenatal alcohol exposure (Astley, 2004; see also Cook et al., 2016; Hoyme et al., 2016 for examples of other diagnostic nomenclature designed to capture the range of disorders falling under the umbrella of FASD). According to Lange et al.' meta-analysis of 24 unique studies (2017), approximately 8 in 1000 children and youth in the general population worldwide have FASD. In the United States, an estimated 1%–5% of the population have FASD (Center for Disease Control and Prevention, 2023). Past studies of FASD have shown difficulty with both expressive and receptive language skills (Aragón et al., 2008; McGee et al., 2009). Indeed, language impairment is one of the more commonly reported outcomes in FASD. For example, Hemingway et al. (2019) found that among 402 individuals with FASD 6 years of age and older, more than three-quarters of individuals with more severe FASD diagnoses (FAS and static encephalopathy) and a quarter of individuals with milder diagnoses (neurobehavioural disorder) presented with significant impairment in language. Many individuals with FASD also struggle with social communication and interpersonal communication (Coggins et al., 2003; Terband et al., 2018; Thorne & Coggins, 2016).

Social communication is typically measured through two approaches: standardised assessment of language use for social purposes (e.g., Test of Pragmatic Language; Phelps-Terasaki & Phelps-Gunn, 2007) and parent/caregiver report. However, prior studies have identified limitations with these assessment methods such as difficulty in using standardised testing for children with autism due to lack of motivation (Koegel et al., 1997) or the presence of bias in caregivers' reports of the child's language (Tomasello & Mervis, 1994). Thus, narrative discourse offers an ecologically valid method of assessing real-world language skills and social communication in autistic individuals (e.g., Levinson et al., 2020) and individuals with FASD (e.g., Proven et al., 2014; Thorne, 2017).

Narrative abilities in autistic individuals

Past studies of language abilities in autistic individuals show that the use of natural language samples provides additional information beyond standardised language assessments (Barokova & Tager-Flusberg, 2020; Charman, 2004; King & Palikara, 2018; Manolitsi & Botting, 2011; Peristeri et al., 2017; Tager-Flusberg et al., 2009). For instance, Manolisi and Botting (2011) found that although autistic children did not show expressive language deficits on standardised tests, narrative assessment revealed difficulty with storytelling and referencing. King and Palikara (2018) further note that despite the fact that many autistic adolescents may score within the average range on standardised assessments, difficulty with higher-level language skills may not be revealed by these assessments. Similarly, as standardised testing often misses important differences that are evident in naturalistic settings, Lee et al. (2018) found the use of computational linguistics in analysing narrative skills to be effective in distinguishing adolescents and adults with autism from comparison participants without autism.

In past studies of narrative discourse, autistic individuals were found to produce shorter and less complex sentences and stories (Banney et al., 2015; Eigsti et al., 2007; King et al., 2014; Tager-Flusberg & Sullivan, 1995), score lower on local language measures by

producing fewer personal pronouns, temporal expressions, referential expressions (Colle et al., 2008; King et al., 2014; Novogrodsky, 2013), mental states and causal statements (Siller et al., 2014; Tager-Flusberg & Sullivan, 1995). Some autistic individuals were also found to produce stories that were biased toward local details (Barnes & Baron-Cohen, 2012). For example, during a narrative task describing a film, autistic participants were more likely to describe the details in a visual scene, such as a computer in the background instead of the overall setting such as a hospital or an office building, as was typically described by the control group (Barnes & Baron-Cohen, 2012). These global details are needed to capture the 'big picture' of the story, which provides meaningful answers to each story element. Thus, autistic individuals may provide details about the setting or characters but may leave out significant information that helps a listener glean meaning from the information (Barnes & Baron-Cohen, 2012).

However, there are still many aspects of narrative abilities in autistic individuals that are not well understood due to inconsistent findings in past literature. Past research has mostly focused on autistic children and adolescents with fewer studies conducted in adults (e.g., Colle et al., 2008; Geelhand et al., 2020; McCabe et al., 2013). Furthermore, many past studies on narrative discourse have included heterogeneous samples, including autistic individuals across a wide range of age, intellectual and/or language abilities. There have been several reports that when groups are matched on age and cognitive abilities, fewer differences between narratives produced by autistic individuals and neurotypical comparisons are observed (e.g., Colle et al., 2008; Diehl et al., 2006; Losh & Capps, 2003; Losh & Gordon, 2014; Tager-Flusberg & Sullivan, 1995). Moreover, while some past literature reports shorter and less complex narratives (Banney et al., 2015; Tager-Flusberg, 1995), other studies find that the narratives produced by autistic individuals are comparable to comparison participants (Losh & Capps, 2003; McCabe et al., 2013; Sah & Torng, 2015). Similarly, while some past studies report that narratives produced by autistic individuals have fewer cohesive devices (Hilvert et al., 2016), others found minimal to no differences in cohesion compared to a matched control group (Kauschke et al., 2016). Colle et al. (2008) found that pragmatic skills in highly verbal autistic adults did not differ from age-, sex- and IQ-matched comparison groups; however, a narrative discourse task revealed specific challenges in autistic individuals such as using fewer personal pronouns, temporal expressions and referential expressions. Many of these previous studies; however, had small sample sizes and differences in how the study participants were matched to the autistic group, which further complicates the picture (Harvey et al., 2023).

Narrative abilities in individuals with fetal alcohol spectrum disorders

Although there are comparatively more studies on narrative discourse in autistic individuals, several studies have similarly explored the utility of narrative discourse as a language assessment method in individuals with FASD (e.g., Thorne, 2017; Thorne et al., 2007; Vega-Rodríguez et al., 2020). Thorne et al. (2007) analysed stories produced by children 8–11 years of age with FASD for semantic elaboration and reference strategy and found that the rate of ambiguous nominal reference was a marker that distinguished children with FASD from age-matched children without FASD. This finding indicated that errors in referential cohesion, which refers to the failure to introduce and maintain references in an organised way that allows the listener to recognise references and follow the story, may be harder for neurodiverse individuals. In addition to referential cohesion, a study by Ganthous et al. (2017) found difficulties with both global and local measures of narratives, including managing structural elements of the story as well as the ability to use diverse vocabulary, to produce appropriately complex sentences. Difficulty avoiding grammatical errors during narrative production may also be common in FASD (Thorne, 2017).

Present study

Since prior studies have noted difficulties in language and social communication for both individuals with FASD and autism (Bishop et al., 2007; Stevens et al., 2013), the approach taken in the current study is to compare the narrative discourse of adolescents and adults across the two groups, as well as an age- and sex-matched comparison group, to better understand the relationship between narrative discourse and language ability across these three groups. With the limited number of studies available, there is a need for more research on narrative discourse in individuals with FASD. Moreover, while there are numerous studies demonstrating difficulty producing cohesive narratives in autistic children, fewer have included adolescents or adults (Beaumont & Newcombe, 2006; Colle et al., 2008; Geelhand et al., 2020). Thus, the specific goal of the present study is to characterise the similarities and differences in the narrative discourse between adolescents and adults from autism, FASD, and neurotypical groups.

We adopted the *Systemic Analysis of Language Transcript* (SALT) convention for the narrative analysis (Miller & Iglesias, 2020) and the Narrative Scoring Scheme (NSS). The NSS total score is meant to serve as an overall assessment of an individual's ability to produce a structurally sound and coherent narrative with a scoring rubric of

seven categories: introduction, character development, mental states, referencing, conflict/resolution, cohesion and conclusion (see Methods section for further details). The SALT software and language analysis approach standardises the process of transcribing and analysing language samples, allowing for comparison to past studies. Besides the NSS total score, SALT includes two categories of measures: local and global. The local aspect of a narrative demonstrates the speaker's ability to integrate and form cohesive connections at the utterance level (within and across sentences) while the global aspects of a narrative demonstrate the speaker's general facility with language across the length of the narrative. Following SALT conventions, the local measures employed in this study include the use of temporal relation and mental state words. The global measures include the mean length of utterance, semantic measures of the number of used word roots, length of narrative (total words), the total number of utterances produced, rate of speech, mazes per total words as well the NSS total score for each story (Miller & Iglesias, 2020). All variables were measured using SALT's built-in tool—*Language Sample Analysis*, that provided a quick and accessible process for transcribing, coding and analysing the language samples. With detailed protocols, minimal coding and utilising computer analyses, SALT standardised the process of analysing language samples, thus giving consistent and reliable measures of narrative language (see Miller et al., 2015).

The overarching question addressed in this study is whether there are differences in the local and global structure of narratives produced by participants in the autism, FASD and comparison groups. Using a matched pairs research design in combination with random and opportunity sampling techniques to recruit age- and sex-matched comparison participants to the autism and FASD group, we asked the following questions:

Question 1: Are there group differences between local structure variables? To address this question, we quantified the number of temporal relations and mental states produced and compared them across autism, FASD, and comparison groups. Based on findings from prior studies, we hypothesised that participants with autism and FASD would perform worse on the local measures in comparison to the group. We further hypothesised that the FASD group would score higher on the local measures than the autism group.

Question 2. Are there group differences between global structure variables? To address this question, we quantified the global features, including mean length of utterance, total different words, total words, total utterances, rate of speech, number of mazes (e.g., repetitions, 'um', 'uh' or self-corrections) per total words and NSS total score and compared across autism, FASD and comparison groups. Despite the inconsistent findings from the literature, based on studies that reported comparable narrative ability of global structures, we hypothesised that participants with autism and FASD would perform similarly on all measures to the neurotypical comparison group.

Question 3. What is the relationship between local and global features of narratives produced? To address this question, we assessed the relationship between each local and global feature.

Question 4. What is the relationship between global features? To address this question, we assessed the relationship between each global feature.

METHODS

Participants

Forty-six individuals participated in the study from three groups: individuals with autism ($n = 12$), individuals with FASD ($n = 11$) and a comparison group ($n = 23$) that were age- and sex- matched to autism and FASD groups (see Table 1 for breakdown of demographic information by groups). Data from one autistic participant was not usable due to poor audio recording quality, resulting in 11 autistic participants being included in the narrative analysis.

Autism group

Twelve participants diagnosed with autism were recruited from a larger longitudinal study of preschool and early school age development conducted at a large university. The original cohort consisted of 72 autistic children initially recruited between 3 and 4 years of age via advertisements in the local community including parent groups, hospital clinics, the University of Washington Autism Center and the University of Washington Infant and Child

TABLE 1 Sample demographic information of autism, FASD and comparison groups.

	Autism	FASD	Comparison
n	11	11	23
Sex			
Female	4 (36%)	6 (55%)	11 (48%)
Male	7 (64%)	5 (45%)	12 (52%)
Age, years			
Mean	21.66	20.60	21.72
Range	20.9-23.16	13.69-47.07	13.16-45.39
SD	0.64	9.86	6.00
Ethnicity			
Not Hispanic or Latino	9 (82%)	8 (73%)	22 (100%)
Hispanic or Latino	1 (9%)	2 (27%)	0
Other/NA	1 (9%)	0	0
Race			
White	7 (64%)	4 (36%)	18 (78%)
Asian	0	0	2 (9%)
Native Hawaiian/Pacific Islander	1 (9%)	0	0
American Indian/Alaskan Native	0	4 (36%)	0
Black or African American	0	2 (27%)	0
More than one race	3 (27%)	0	2 (9%)

Abbreviation: FASD, fetal alcohol spectrum disorders.

Subject Pool (see Dawson et al., 2004 for more details). Diagnoses of autism, according to criteria from the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994), were made at 3 years of age by a licensed clinical psychologist or supervised graduate student using: (1) the Autism Diagnostic Interview-Revised (Lord et al., 1994), (2) the Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord et al., 2000), (3) medical and family history, (4) cognitive test scores and (5) clinical observation and judgement (see Dawson et al., 2004; Emmons et al., 2021 for further details). These participants were evaluated again at 6, 9 and 13–15 years of age. Specific inclusion criteria for this present study included passing an audiometric screening for clinically normal hearing thresholds, being able to speak in three-word phrases, IQ > 80 and having no other health or developmental concerns. Normal hearing is an important criterion since autistic individuals have a higher incidence of hearing loss (e.g., Rosenhall et al., 1999; Szymanski et al., 2012), which could also affect language abilities. Forty-six participants from the original cohort were re-contacted and invited to participate in this current study. The remaining 26 were not contacted because they had been randomly recruited for another study. Of the 46 participants contacted, four had moved out of state, two were not interested in participating, one could not be scheduled, 25 did not respond to phone calls or emails and two did not meet our eligibility criteria of being able to speak in three-word phrases. Twelve autistic participants from the original cohort were enrolled in this study and tested at ages 21–23 years of age (see Table 1 for sample demographic information).

FASD group

Eleven participants diagnosed with FASD were recruited from the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network, a database of individuals who have received assessments for FASD. Prenatal alcohol exposure was confirmed through (1) direct observation of drinking, (2) lab tests (blood alcohol) during pregnancy or delivery or (3) full face of FAS. During routine clinic visits, participants were provided with information about the current research study and given the option to participate, if interested. All participants were diagnosed using the FASD 4-Digit Diagnostic Code, which is an interdisciplinary approach to diagnose the full spectrum of outcomes guided by the magnitude of expression of the four features of FAS: growth deficiency, FAS facial phenotype, CNS structural/functional abnormalities and prenatal alcohol exposure (Astley, 2004; see McLaughlin et al., 2019 for more details). There are four diagnoses that fall under the umbrella of FASD: FAS, Partial FAS (PFAS), SE/AE, ND/AE. No participants in the FASD group received an ADOS autism classification. As with

the autism group, inclusion criteria for the FASD group included passing an audiometric screening for clinically normal hearing thresholds, being able to speak in three-word phrases, IQ > 80 and having no other health or developmental concerns. Ten of 11 FASD participants were adolescents and adults between the ages of 13 and 23; however, one 47-year-old female was also included in the study. The FASD group included two individuals with FAS, one with SE/AE and eight with ND/AE.

Comparison group

The comparison group consisted of 23 participants, who were recruited through flyers distributed around the university and the greater Seattle community. For each participant in the autism and FASD group, one age- and sex-matched participant was recruited as a pair-matched comparison participant. Age matching in comparison participants was ±1 year with one exception: a 47-year-old participant in the FASD group was matched to a 45-year-old comparison individual. Participants were also matched on sex to reflect the higher incidence of males with a diagnosis of ASD (Maenner et al., 2023). Comparison group participants all reported no history of cognitive, developmental or other health concerns. Two participants in the comparison group had a diagnosis of attention-deficit/hyperactivity disorder (ADHD) but were included because there were individuals with ADHD in both the autism and FASD groups. No participants in the comparison groups received an ADOS autism classification.

Procedure

The following measures were obtained over the course of several visits and as part of a larger study that included additional neurophysiological and behavioural measures. Written informed consent was obtained from all participants or their legally authorized representative for participants under 16 years of age. All methods were performed in accordance with protocols reviewed and approved by the Institutional Review Board at the University of Washington where the research was conducted. Participants were provided with monetary compensation for their time.

ADOS-2

The ADOS-2 (Lord et al., 2012), a measure of autism symptom severity, was administered to all participants at the time of testing to confirm autistic status in all participant groups. All participants in the autism group received an ADOS classification of autism. No participants in the comparison or FASD groups received an ADOS autism classification.

WASI-II

The Wechsler Abbreviated Scale of Intelligence—Second Edition (WASI-II; Wechsler, 2011), a measure of intellectual ability, was administered to all participants. Four subtests: Block Design, Vocabulary, Matrix Reasoning and Similarities, were administered to compute the WASI-II Full Scale Intelligence Quotient-4 for each participant and provide an overall estimate of intellectual functioning. The Verbal Composite Index score was computed from the Vocabulary and Similarities subtests and the Perceptual Reasoning Index scores were computed from the Block Design and Matrix Reasoning subtests (see Table 2 for score breakdown).

Auditory screening

To ensure clinically normal hearing thresholds in all participants, each participant was required to pass an audiometric screen (≤20 dB hearing level at octave frequencies between 500 and 8000 Hz), a distortion product otoacoustic emission screen, and an auditory brainstem response screen.

Elicitation of narratives

The 24-page wordless book, *Frog, Where Are You?* (Mayer, 1969), was used to elicit narrative language samples. This story has been used in previous research with both children and adults (Colle et al., 2008) and does not require any prior descriptions or specific prompts from the examiner. This wordless picture book requires the narrator to connect and organise different actions from the protagonists and events into a coherent story, providing a measure of temporal expressions. Because the story does not provide verbal cues, the participants have the freedom to explore the characters' inner states by taking the perspective of the characters and communicating them to the listener. The story is about a young boy and his dog in search of his lost pet frog. The protagonists' search involves numerous events and encounters with secondary characters. Throughout the story, the two characters engage with these secondary characters in developing the story to finally find the lost pet frog.

Each participant was assessed individually, and each narration was audio recorded for transcription and

TABLE 2 Sample characteristics: WASI-II score, story length by autism, FASD and comparison groups.

		Autism	FASD	Comparison
WASI-II FSIQ-4	*M*	102.36	97.00	119.91
	SD	(14.33)	(19.89)	(6.30)
WASI-II VCI	*M*	98.27	98.70	116.05
	SD	(23.44)	(19.56)	(8.25)
WASI-II PRI	*M*	104.91	95.50	119.09
	SD	(8.99)	(17.49)	(9.34)
Story length	Range	0:49–5:02	1:45–4:59	0:57–2:59
(min:s)	*M*	3.07	2.74	1.80

Abbreviations: FASD, fetal alcohol spectrum disorders; FSIQ-4, Full Scale Intelligence Quotient-4; PRI, Perceptual Reasoning Index; VCI, Verbal Composite Index; WASI-II, Wechsler Abbreviated Scale of Intelligence–Second Edition.

analysis. Participants were presented with a copy of the wordless book *Frog, Where Are You*? A divider was placed between the examiner and the participant so that the examiner was unable to see the pictures in the book while the participant was telling the story. The examiner instructed the participants to review the pictures in the book to become more familiar with the story and then they were asked to use the pictures as a visual prompt to tell the best story that they could. After the participant looked through the book, the examiner confirmed that they were ready and had them turn back to the first page of the book to start recording the story. The participant went through each page of the book and told the story without any prompts provided. The examiner did not intervene during the narration. However, when necessary, the examiner was permitted to provide a verbal prompt to help the participant get started (e.g., 'I will help you get started, once upon a time there was . . . ') or encourage the participant throughout the storytelling (e.g., 'What happened next?'). This procedure ensured that the participants did not memorise the story and emphasised the storytellers' ability to anticipate the listener's informational needs. After the participants finished telling the story, the examiner stopped the recording and praised the participants for their storytelling skills.

Transcription of narratives

Narratives were transcribed orthographically and formatted according to SALT conventions. Transcripts were segmented into *Communication units* (C-units). A C-unit is an independent clause with its modifiers, which includes one main clause with all subordinate clauses attached to it (Miller & Iglesias, 2020). As subordinate clauses depend on the main clause to make sense, they cannot be separated from the main clause, whereas the main clause can stand alone and can be segmented into C-units. Mazes, such as filled pauses, repetitions and revisions, along with unintelligible utterances, and irrelevant comments were marked and included in the transcription. Using SALT software (Miller & Iglesias, 2020), the transcribed narratives, including the C-units and marked mazes, were later used to analyse structural language properties of the transcription including mean length of utterance, total utterances, total different word roots, total words, rate of speech, mazes (e.g., word repetitions or 'um', 'uh') per total words and the overall NSS total score. Details of the transcription can be found on the SALT Training Website (Salt Software, n.d.).

Coding of narratives

The transcribed narratives were entered into the SALT software (Miller & Iglesias, 2020), which aids the process of analysing words, morphemes, utterances and discourse, and were used to code and analyse structural language properties. Codes from SALT was used to calculate the mean length of utterance, total utterances, total different word roots, total words, rate of speech, mazes (e.g., word repetitions or 'um', 'uh') per total words and the overall NSS total score. Additional codes were created to measure the use of mental state and temporal relation words. Two coders were trained on transcription and SALT coding, including the NSS total score and the identification of mental state and temporal relation words using two separate training stories. They were required to achieve over 80% agreement for both transcription and coding with a third experienced coder on the training stories before moving on to the actual data set.

Temporal Relations. The total number of temporal expression terms, excluding mazes, were counted to assess if participants with autism and FASD could organise events in sequential order. Temporal relation terms included temporal adverbs and conjunctions such as 'last night', 'yesterday', 'now' and 'meanwhile'.

Mental States. The total number of mental state terms, excluding mazes, were counted, which included the emotional state of a character in the story (e.g., 'The boy

is *angry* at the dog') and any reference to a mental state, including emphasising the character to explore their inner thoughts, beliefs, intentions (e.g., 'The boy *thought* the frog ran away').

NSS Score. Each of the narrative stories was then coded using the NSS total score as described in the SALT Training Website (n.d.). The NSS total score assesses the individual's ability to produce a structurally sound and coherent narrative. The scoring guideline included many features of story grammar including cohesiveness, connection of story events, consideration for characters' thoughts and behaviours and referencing. Each story was graded on a rubric of seven categories with a grading scale of 0–5: introduction, character development, mental states, referencing, conflict/resolution, cohesion and conclusion. Categories that could not be scored received a score of zero or N/A. Scores of zero were given for the target speaker errors (e.g., not following the protocols or telling the wrong story), and a mark of non-applicable (N/A) was given for the examiner errors (e.g., interference with the speaker's story or recording issues). For each section, a score of 1 indicated minimal/immature performance, a score of 3 indicated emerging skills and the highest score of 5 indicated proficient characteristics. Scores of 2 and 4 were undefined and given based on the examiner's judgment with justification. The scores for each section were then combined to give a total narrative score with the highest possible score of 35. For more details on scoring and guidance using the NSS, see the SALT training website (n.d.).

Interrater agreement

To ensure the reliability of the data, a systematic process of transcription and scoring was designed to prepare all narratives from recorded sourced files by two researchers. The secondary researcher was not informed of the group identity or diagnosis of the narrator. Interrater reliability was calculated for all measures with 93% agreement on words and 89% agreement on C-units in terms of transcription and 96% agreement on all categories of the NSS total score. Percent agreement on words and C-units was calculated based on the number of differences in terms of the numbers of words and C-units. Percent agreement on the NSS total score was determined for each of the seven category scores independently. In each category, the score had to be within ±1 point for the primary and secondary coders to be considered in agreement. The percent agreement between the primary and secondary coder was high across categories; introduction: 93%, character development: 98%, mental states: 96%, referencing: 91%, conflict/resolution: 100%, cohesion: 100% and conclusion: 96%. Since a high percent agreement was achieved, the scores determined by the secondary coder were used to avoid the first coder's biases, who is an author on the manuscript.

Statistical analysis

Pair matching was conducted during the recruitment of the comparison group participants to achieve a balance in age and sex between the study groups. A two-tailed Fisher's exact test revealed a reasonably balanced gender profile across groups ($p = 0.53$; see Table 1 for more details). A Kruskal–Willis test, used due to unequal variance between the groups, revealed no significant difference in the age distribution across groups ($c^2 = 2.29$, $df = 2$, $p = 0.32$; see Table 1 for more details). Thus, this pair matching was not maintained in the statistical analyses because preliminary analyses conducted detected no significant group differences in age or gender.

All analyses were conducted using the same sample size ($N = 46$; autism, $n = 11$; FASD, $n = 11$; comparison, $n = 23$. To test the main hypothesis of whether there were differences in the local and global structure of narratives produced, a one-way analysis of variance (ANOVA) was used to test for statistical differences between the means across all the groups. To assess the relationship between local and global variables, Pearson correlation coefficient (Pearson's r) was used to measure the strength of the linear relationship between the number of temporal relation words produced as well as between mental state words produced and other global measures. Finally, Pearson's r was also used to investigate the relationship between different global measures of the narratives.

RESULTS

Local measures across groups

To address our first research question, Table 3 shows the means and standard deviations for the two measures of local abilities, temporal relation words and mental state words. A one-way ANOVA revealed no statistically significant group differences in the number of mental state words produced (Figure 1b; one-way ANOVA, $F(2,42) = 0.54$, $p = 0.59$, $\eta^2 = 0.02$) or temporal relation words produced (Figure 1a; one-way ANOVA, $F(2,42) = 1.85$, $p = 0.17$, $\eta^2 = 0.08$).

Global measures across groups

Table 4 presents the means and standard deviations for five measures of global abilities including total words produced, rate of speech, number of mazes produced per total words, number of different words produced, mean

TABLE 3 Local measures raw scores: Means, SDs, and one-way ANOVA comparisons between autism, FASD and comparison groups.

Local measures	Autism		FASD		Comparison		$F(2,42)$	η^2
	M	*SD*	*M*	*SD*	*M*	*SD*		
1. Temporal relation words	11.50	7.28	8.09	3.33	8.13	4.30	1.85	0.08
2. Mental state words	6.82	2.71	5.46	3.27	5.83	3.46	0.54	0.02

Abbreviations: ANOVA, analysis of variance; FASD, fetal alcohol spectrum disorders.

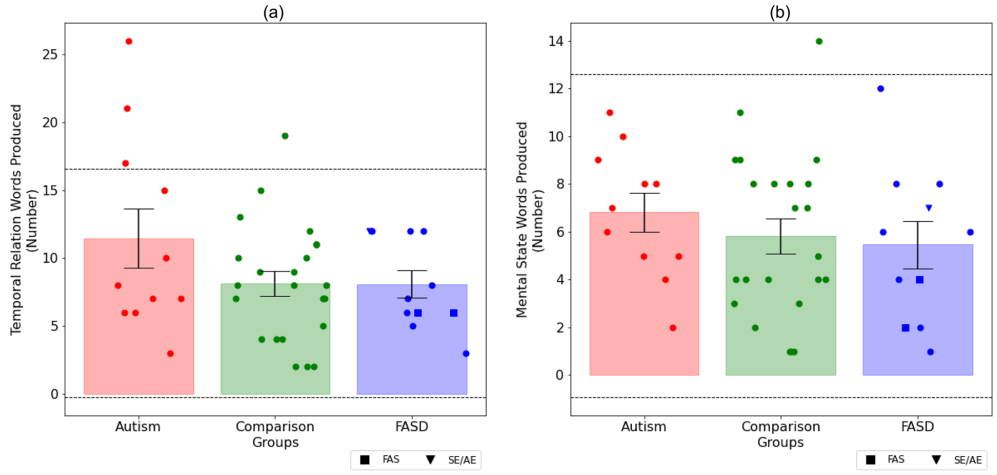

FIGURE 1 Local measures, temporal relation words (a) and mental state words (b), as a function of participant group. Mean ± SE shown with bars. Individual data points shown with solid circles. Dotted lines show ±2 SD of the Comparison group mean as reference. Square marker shows participants with Fetal Alcohol Syndrome (FAS) and triangle marker shows participants with Static Encephalopathy, Alcohol Exposed (SE/AE). No group differences were observed for the number of temporal relation and mental state words produced. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Global measures raw scores: Means, SDs, and one-way ANOVA comparisons between autism, FASD and comparison groups.

Global measures	Autism		FASD		Comparison		$F(2,42)$	η^2
	M	*SD*	*M*	*SD*	*M*	*SD*		
1. Total words with mazes	381.55	125.67	314.09	124.15	283.91	97.31	2.86	0.12
2. Words/minute	128.90	23.07	115.19	28.24	159.04	20.43	15.35**	0.42
3. Mazes/total words	0.12	0.08	0.06	0.05	0.04	0.03	8.82**	0.30
4. Total different words	119.91	31.04	106.55	27.03	104.57	26.42	1.19	0.05
5. Mean length of utterances	11.26	2.98	9.74	1.72	10.40	1.89	1.38	0.06
6. Total utterances	31.18	12.68	30.82	14.21	25.87	7.09	1.32	0.06
7. NSS total score	24.91	5.30	22.27	6.42	22.74	4.61	0.84	0.04
8. NSS conflict	4.09	1.38	3.09	1.38	3.00	0.85	3.68*	0.15

*$p \leq 0.05$.
**$p \leq 0.001$.
Abbreviations: ANOVA, analysis of variance; FASD, fetal alcohol spectrum disorders; NSS, Narrative Scoring Scheme.

length of utterances in words, total utterances produced and the NSS total score. A one-way ANOVA comparing each of the global measures in the autism, FASD and comparison groups revealed significant differences in the rate of speech and mazes per total words but no significant group differences in total words produced, number of different words produced, mean length of utterance or NSS total score. Of the seven categories that contribute to the

NSS total score, significant group differences were also observed for conflict/resolution,

Rate of speech. The comparison group spoke with a faster rate of speech, measured by the number of words spoken per minute, compared to the autism and FASD groups (Figure 2b). A one-way ANOVA revealed a significant difference across groups in the number of words spoken per minute (one-way ANOVA, $F(2, 42) = 15.35$, $p < 0.001$, $\eta^2 = 0.42$). Post-hoc comparisons using independent sample *t*-tests with Bonferroni correction revealed a lower rate of speech in the autism ($M = 128.90$, $SD = 23.07$) and FASD ($M = 115.19$, $SD = 28.24$) groups compared to the comparison group ($M = 159.04$, $SD = 20.43$). However, no significant difference was observed between the autism and FASD groups. Notably, four of the individuals with autism and four from the FASD group (one with FAS) spoke at a rate more than 2 SD slower than the mean of the comparison group (See Figure 2b).

Number of mazes per total words. The number of mazes produced per total words showed that the autism group produced more mazes (e.g., repetition, 'um', 'uh') compared to the FASD and comparison groups (see Figure 2c). A one-way ANOVA revealed a significant group difference in the number of mazes per total words (one-way ANOVA, $F(2,42) = 8.82$, $p < 0.001$, $\eta^2 = 0.30$). Post-hoc comparisons were conducted using independent sample *t*-tests with Bonferroni correction, which revealed a significantly higher number of mazes produced per total words in the autism group ($M = 0.12$, $SD = 0.08$) compared to the comparison group ($M = 0.04$, $SD = 0.03$) and to the FASD group ($M = 0.06$, $SD = 0.05$). However, no significant group difference was detected between the FASD and comparison groups. Notably, the autism group had a much wider variability in the maze words per total words and the mean from the autism group on this measure was more than 2 SD higher than the mean of the comparison group (See Figure 2c).

NSS conflict/resolution. To generate the NSS total score, an estimate of the overall score of whether the story is structurally sound and coherent, each story was graded on a rubric of seven categories. The NSS category score for conflict/resolution showed that the autism group scored higher compared to the FASD and comparison groups (Figure 2h). A one-way ANOVA revealed a significant group difference in the score of conflict/resolution (one-way ANOVA, $F(2,42) = 3.68$, $p = 0.03$, $\eta^2 = 0.15$). Post-hoc comparisons were conducted using independent sample *t*-tests with Bonferroni correction, which revealed a significantly higher score for conflict/resolution in the autism group ($M = 4.09$, $SD = 1.38$) compared to the comparison group ($M = 3.00$, $SD = 0.85$). However, no significant group difference was observed between the autism and FASD groups ($M = 3.09$, $SD = 1.38$) or between the FASD and comparison groups. Notably, six from the autism group and three from the FASD group received the highest possible score on this measure (i.e., a score of 5), where only one individual from the comparison group performed as well (See Figure 2h).

Relationships between local measures and global measures

To investigate the relationship between local and global measures of the narratives, Pearson correlation coefficient (Pearson's r) was used to measure the strength of the linear relationship between the number of temporal relation words produced as well as between mental state words produced and other global measures (see Table 5). This revealed a positive correlation between the NSS total score and the number of temporal relation words (Pearson's r, $r(43) = 0.38$, $p = 0.01$) and between NSS category conflict/resolution and the number of temporal relation words (Pearson's r, $r(43) = 0.49$, $p < 0.001$). The higher the overall NSS score or NSS conflict/resolution, the greater the number of temporal relation words observed. A positive correlation between NSS total score and the mental state words as well as NSS category conflict/resolution was also detected (NSS total score, Pearson's r, $r(43) = 0.63$, $p < 0.001$; NSS conflict/resolution, Pearson's r, $r(43) = 0.47$, $p < 0.001$). The higher the overall NSS score and its conflict/resolution category, the more mental state words are observed.

Relationships within global measures

To investigate the relationship between different global measures of the narratives, Pearson correlation coefficient (Pearson's r) was also used (see Table 6). A strong correlation between the number of total words produced and the number of mazes produced per total words (Pearson's r, $r(43) = 0.33$, $p = 0.03$) was observed, which indicates a higher number of mazes was observed for longer narratives. The rate of speech was also positively correlated with mean length of the utterances (Pearson's r, $r(43) = 0.36$, $p = 0.01$), which suggests that the longer the length of the utterances, the faster the rate of speech. Additionally, a strong correlation between NSS category conflict/resolution and a few other global measures were also observed, including total words with mazes (Pearson's r, $r(43) = 0.80$, $p < 0.001$), total different words (Pearson's r, $r(43) = 0.79$, $p < 0.001$), mean length of utterances (Pearson's r, $r(43) = 0.35$, $p = 0.02$), total utterances produced (Pearson's r, $r(43)$

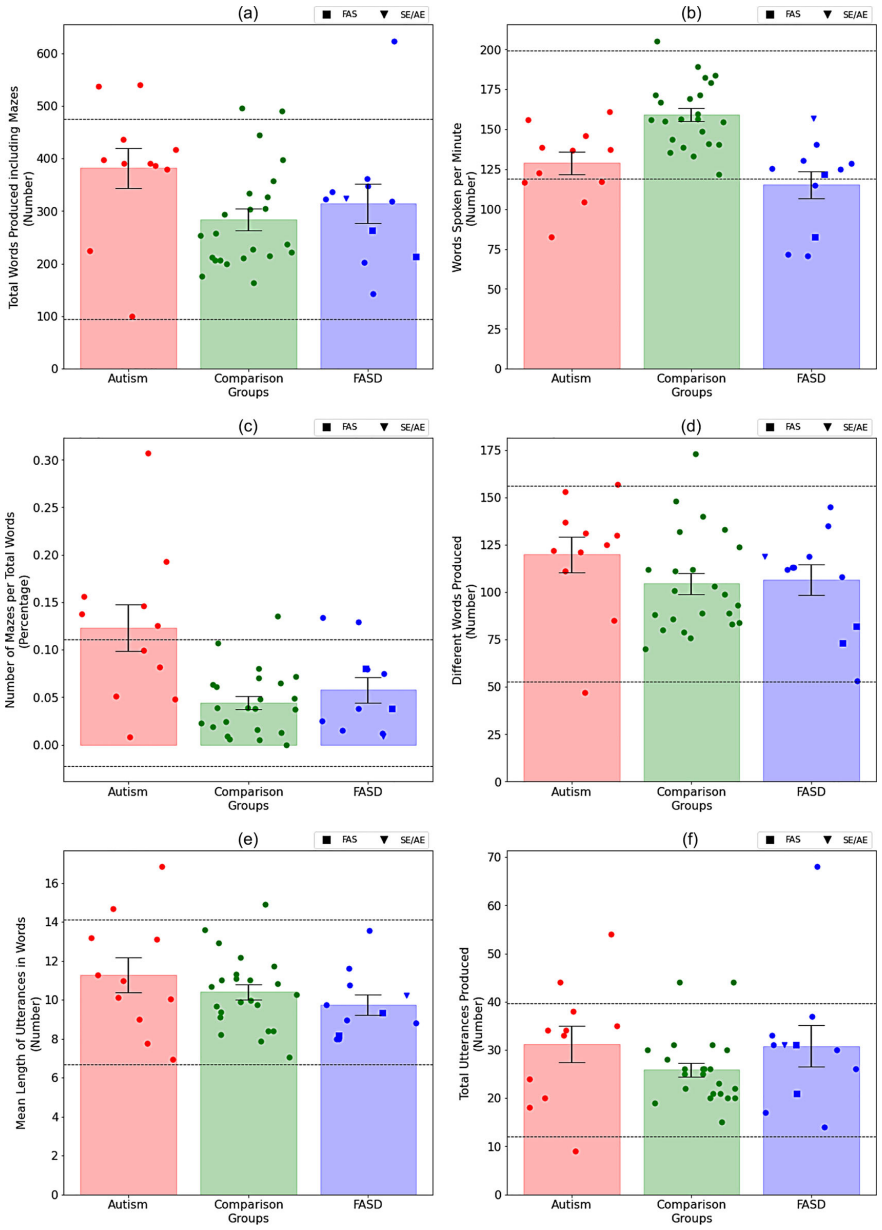

FIGURE 2 Global measures: total words produced (a), words spoken per minute (b), number of mazes per total words (c), different words produced (d), mean length of utterances in words (e), total utterances produced (f), Narrative Scoring Scheme (NSS) total score (g) and NSS conflict/resolution as a function of participant group (h). Mean ± SE shown with bars. Individual data points shown with solid circles. Dotted lines show ±2 SD of the Comparison group mean as reference except in (g) and (h). For (g) dotted lines show NSS total score normative ranges; Proficient: 35–28, Emerging: 14–21, Immature: 0–7. For (h) dotted lines show NSS total score normative ranges; Proficient: 5, Emerging: 3, Immature: 1. Square marker shows participants with Fetal Alcohol Syndrome (FAS) and triangle marker shows participants with Static Encephalopathy, Alcohol Exposed (SE/AE). Group differences were observed for words spoken per minute, number of mazes per total words and NSS category conflict/resolution. [Colour figure can be viewed at wileyonlinelibrary.com]

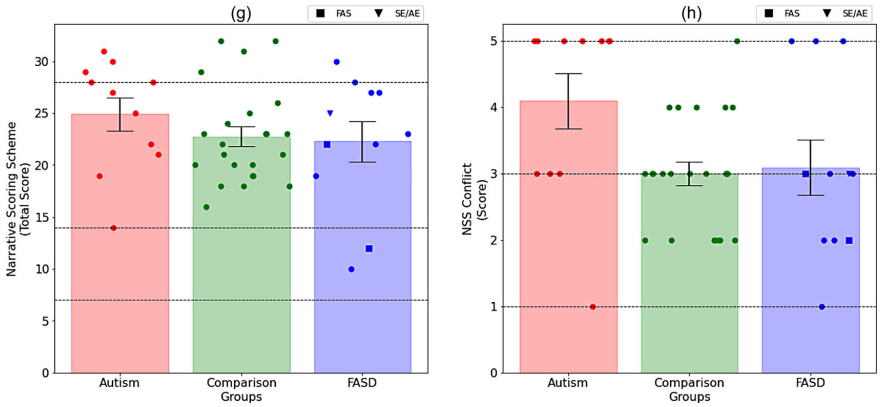

FIGURE 2 Continued

TABLE 5 Correlations between local measures and global measures.

Global variables	Local variables	
	Temporal relation	Mental state
1. Total words with mazes	0.62***	0.60***
2. Words/minute	0.10	0.21
3. Mazes/total words	0.10	0.08
4. Total different words	0.51***	0.66***
5. Mean length of utterances	0.36*	0.44**
6. Total utterances	0.38**	0.40**
7. NSS total score	0.38**	0.63***
8. NSS conflict	0.49***	0.47***

*$p \leq 0.05$.
**$p \leq 0.01$.
***$p \leq 0.001$.
Abbreviation: NSS, Narrative Scoring Scheme.

$= 0.63$, $p < 0.001$) and NSS total score (Pearson's r, $r(43) = 0.81$, $p < 0.001$).

DISCUSSION

In this study, we elicited narratives using a wordless picture book to investigate narrative discourse abilities in a sample of adolescent and adults with autism, FASD and an age- and sex-matched comparison group. We evaluated both local and global language features of the narratives produced and group differences were observed on three global measures: the number of mazes per total words produced, rate of speech, as well as the conflict/resolution category score that contributed to the NSS total score. Participants in the autism group produced significantly more mazes per total words compared to the FASD and comparison groups, and both the autism and FASD groups spoke at a lower rate of speech compared to the comparison group (i.e., talked slower). Participants in the autism group also scored significantly higher than the FASD and comparison group on the NSS category score for conflict/resolution. No significant group differences were found on local measures, including the number of temporal relation and mental state words produced. While our findings revealed that at the group level, many aspects of global narrative production, including the total number of words including mazes, number of different words, total number of utterances, mean length of utterances, the NSS total score in the autism and FASD groups were comparable to the comparison group, there was notable variability within each group.

The control of local and global aspects of language contributes to successful social communication and narrative discourse as the speakers are required to consider a listener's perspective to construct a cohesive narrative as they organise the story. Our results addressed the broad question: are there differences in the local and global structure

TABLE 6 Correlations between global measures.

Global variables	1	2	3	4	5	6	7
1. Total words with mazes	—						
2. Words/minute	0.04	—					
3. Mazes/total words	0.33*	−0.23	—				
4. Total different words	0.90***	0.13	0.14	—			
5. Mean length of utterances	0.37**	0.36**	0.12	0.58***	—		
6. Total utterances	0.79***	−0.15	0.13	0.60***	−0.23	—	
7. NSS total score	0.73***	0.19	−0.02	0.84***	0.53***	0.45**	—
8. NSS conflict/resolution	0.80***	0.01	0.10	0.79***	0.35*	0.63***	0.81***

*$p \leq 0.05$.
**$p \leq 0.01$.
***$p \leq 0.001$.
Abbreviation: NSS, Narrative Scoring Scheme.

of narratives produced by participants from the autism, FASD and comparison groups? Each of these findings is discussed in more details later.

Local measures

Temporal relations

At group level, there was no significant difference observed in the number of temporal relation words produced by autism, FASD and comparison groups. This finding is in contrast with Colle et al. (2008), who did find a difference between the autism and comparison groups. Additionally, we observed a positive correlation between the NSS total score as well as the NSS category conflict/resolution score and the number of temporal relation words, indicating that the more temporal relation words produced, the more coherent the story and the better the conflict and resolution. A positive correlation between the number of total words (including mazes) and the number of temporal relation words was also observed, which indicates that the number of temporal words produced was proportional to the length of the story itself but may not necessarily tell us about how participants maintained and used temporal references. Given the strong relationship between the number of temporal relation words produced and the NSS total score, the use of temporal relation words may have helped the storytellers produce a more coherent story. Thus, this finding suggests that the number of temporal relation words produced may be a good predictor for the storyteller's overall ability to produce a coherent narrative.

Mental states

Our results also did not show any significant differences at group level between the autism, FASD and comparison groups in the production of mental state words. This, however, was not what we predicted. These findings were consistent with some of the results from the narrative discourse of autistic individuals in both adults (Beaumont & Newcombe, 2006; Colle et al., 2008; Suh et al., 2014) and children (Tager-Flusberg & Sullivan, 1995). However, although Tager-Flusberg and Sullivan (1995) showed that autistic children produced a similar quantity of emotional and mental state words, they noted that autistic children were more likely to use expressions with a limited understanding of intentions and internal states of the character and less likely to take into consideration the point of view of the listener. Similarly, Beaumont and Newcombe (2006) found no differences in the number of mental state words produced, but adults with autism were less likely to provide an explanation as to why a character was thinking or feeling in a particular way compared to comparison participants. In short, these children were able to label emotions but did not fully understand the role of the mental state expressions that they used. This finding suggests that although autistic individuals may produce the same number of mental state words as the comparison group, they may show difficulty in comprehension that is not captured by the measures employed in this study.

Nevertheless, a strong correlation between the overall score of NSS as well as its category conflict/resolution and the number of mental state words produced was observed, which indicates that the use of mental state words may help aid in the production of a coherent story.

Global measures

The results showed significant group differences between autism, FASD and comparison participants on the number of mazes per total words, rate of speech and the NSS category score for conflict/resolution. The finding that autistic

individuals produced narratives with greater number of mazes per total words compared to FASD and comparison groups is consistent with past studies that found excessive production of mazes in autistic individuals (Lake et al., 2011; Suh et al., 2014). The slower rate of speech in both autism and FASD compared to the comparison group is also consistent with past studies that found a relationship between low processing speed and communication symptoms in autistic individuals (Haigh et al., 2018; Hedvall et al., 2013; Oliveras-Rentas et al., 2012) and individuals with FASD (Burden et al., 2005; Olson et al., 1998).

Additionally, higher scores on the NSS category score for conflict/resolution of the narratives observed in the autism group revealed the individuals' ability to clearly state all these critical details that help advance the plot of the story (Miller & Iglesias, 2020). These findings are not consistent with past studies that found children with autism produced globally impoverished stories compared to their comparison participants, including a lower score on NSS overall and conflict/resolution specifically (King et al., 2014; King & Palikara, 2018). In our study, participants in the autism group received higher scores compared to the FASD and comparison groups, contrary to our initial expectations.

On other aspects of the global features, the results showed that the autism and FASD groups were comparable to each other as well as the comparison group, including the length of narrative, mean length of utterances, total utterances, total different words produced and the NSS total score. The results on the number of total words produced including mazes are consistent with past studies that found a comparable length of narrative between autism and comparison group (Banney et al., 2015; Colle et al., 2008; King et al., 2014; Suh et al., 2014; Tager-Flusberg & Sullivan, 1995). The results on other measures are consistent with Reindal et al. (2021) as well as Colle et al. (2008)'s findings that autistic children had comparable structural language skills to neurotypical children such as choice of vocabulary. However, since pragmatic language difficulty was found to be more prevalent in autistic children compared to neurotypical children and is an essential component of social communication, pragmatic language skill should be examined in relation to the structural components of narrative discourse.

A particular strength of this study is the multi-group approach, which enabled us to compare the narrative discourse in individuals with autism and FASD. Such examination increases the generalisability of findings to the broader population of adults evaluated for autism and FASD since the literature on narrative discourse in FASD is still limited.

A limitation of this study is that only group-level analyses were conducted due to the small sample size. While our findings suggest strong narrative abilities for the participants in the autism and FASD groups on average in our participant sample, there was also significant variability across individuals. Such heterogeneous results suggest that language abilities need to be considered at the individual level as opposed to the diagnostic category and that our observed results may not generalise to all individuals with autism and FASD. Importantly, individual data with normative reference lines for ±2 SD of the comparison group are presented in Figures 1 and 2 so that one could consider what magnitude of contrast would be clinically meaningful for each subject across diagnostic categories, in addition to what was statistically significant at group level. For the NSS total score and the NSS Conflict/Resolution score, normative ranges were also included in Figure 2 (see figure caption for further details).

In this current study, since we expected heterogeneity in language and intellectual ability in both autism and FASD groups, we measured both verbal and non-verbal intellectual abilities using the WASI—Second Edition (see Table 2). Given the widely distributed performance in both local and global levels of narrative language production, future studies should recruit larger participant numbers and also assess their participants based on their groups' distinctive characteristics or co-occurring conditions such as shape bias in individuals with autism (Abdelaziz et al., 2018) or attention deficit in individuals with autism (Baixauli et al., 2017) and FASD (Nanson & Hiscock, 1990; Rasmussen et al., 2010). Additional variables that influence narrative discourse, such as motivation, distractibility and decision making of individual participants should also be considered.

An additional limitation of this study is that only one storytelling task was obtained, which may not reflect how each individual would perform across different settings in daily social communication situations. It is important to note that although there are aspects of narrative discourse that the participants in this sample did not show difficulty with on this particular task, they may show difficulty with other higher-level language measures. Moreover, the findings reported in this study may not generalise to other individuals with autism and FASD or even other types of narratives within the same participant. Additional tasks and analyses involving narrative discourse would provide useful comparisons between these two groups. Lastly, when context is used to support other structural components of language (e.g., providing temporal relation terms to make a smoother transition between parts of a story or using non-linguistic signals to communicate; Barokova & Tager-Flusberg, 2020), more than just spoken language is used to deliver stories. As such, future studies of narrative discourse in individuals with FASD and autism should be extended to all components of language,

including but not limited to, expressive or pragmatic language skills.

A further limitation of the study is that the majority of the FASD cases were at the moderate end of the spectrum (eight with ND/AE) while only three were at the severe end (two with FAS, one with SE/AE). If the study sample contained only those with FAS/PFAS or SE/AE, we may have identified more significant contrasts. Nonetheless, given the limited number of past studies on the narrative discourse of adolescents and adults with FASD and their shared characteristics with autism (Kippin et al., 2022; Stevens et al., 2013; Terband et al., 2018), this present investigation of narrative discourse will contribute to what we know about the language abilities of individuals with FASD. This study suggests that many aspects of the narrative discourse of individuals with autism and FASD in our particular sample are comparable to the neurotypical comparison participants and each other when considered at the group level. This includes both local and global features. With the comparatively large body of research available in autistic individuals, the results highlighting the similarities between autism and other neurodiverse populations like FASD could lead to more research that is focused on the representations of autistic characteristics in other neurological conditions (e.g., Stevens et al., 2013), and specifically its potential influence on the development of language skills.

Ultimately, the results of this study could aid in the development of clinical tools to best assess language abilities across populations. This understanding could also lead to the development of language support systems that further help individuals advance their language skills and gain self-confidence in daily social communication (Nanson & Hiscock, 1990). Taken together, this current study provided evidence that narrative assessment is an appropriate tool that can be included in routine clinical assessments of language that may reveal important aspects of higher-level language skills required in everyday real-world conversational interactions.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

Data are available from corresponding author upon request.

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Developmental, sensory and behavioral outcomes among infants and toddlers with prenatal alcohol exposure

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ABSTRACT

Background: Prenatal alcohol exposure (PAE) can disrupt children's neurodevelopment and exert lasting influences on overall child well-being and family functioning. A comprehensive exploration of developmental outcomes in infants/toddlers with PAE seen for a diagnosis on the fetal alcohol spectrum can inform early identification and intervention.
Aims: To describe the prevalence and patterns of neurodevelopment, sensory processing, and emotional and behavioral functioning in a clinical sample of infants/toddlers with PAE.
Methods: In this retrospective analysis, clinical data from 125 infants/toddlers with PAE, aged 2–42 months, assessed at the University of Washington Fetal Alcohol Syndrome Diagnostic and Prevention Network clinic were analyzed.
Results: Seventy-four to 87% of infants/toddlers demonstrated delayed development in one or more domains of the Bayley Scales of Infant and Toddler Development (n = 125). Adverse developmental outcomes were significantly correlated with PAE and/or postnatal risk factors. All 93 infants/toddlers with a complete Infant/Toddler Sensory Profile obtained definite difference scores in at least one quadrant/section. Over half of infant/toddlers with a completed Child Behavior Checklist/1½– 5 had total problem scores in the borderline or clinical range.
Conclusions: Findings suggest that several domains of child functioning may be vulnerable to the teratogenic impact of PAE, and that these delays are evident in the first years of life. Early screening, ongoing monitoring and comprehensive assessment is needed to facilitate earlier identification and guide clinical intervention.

What this paper adds?

Prenatal alcohol exposure (PAE) appears to be under-recognized by early childhood practitioners. Challenges related to effective

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screening processes, as well as difficulties detecting early delays or problems in the absence of physical features, may be inhibiting the early identification and intervention of infants/toddlers with PAE. Intervening early can buffer against the developmental vulnerability and postnatal adversity associated with PAE and optimize child and family outcomes in the long term. A comprehensive exploration of developmental, sensory processing and behavioral outcomes in young children seen in a Fetal Alcohol Spectrum Disorder (FASD) diagnostic clinic for individuals with PAE can inform early identification and intervention practices.

Clinically significant developmental delays were highly prevalent in this sample of infants/toddlers with PAE. These adverse developmental outcomes were significantly correlated with PAE and/or postnatal risk factors. Atypical sensory processing behaviors in at least one area were reported for every infant/toddler in the clinical sample. Over half of infants/toddlers presented with emotional and behavior problems outside of the normal range. Present findings, considered with similar studies reported in the literature, suggest that most domains of child functioning are vulnerable to the teratogenic impact of PAE and that these delays are evident in the first years of life. Findings reinforce the value of early screening, ongoing monitoring, and comprehensive assessment to facilitate earlier identification and to provide opportunities for infants/toddlers with PAE and their caregivers to benefit more fully from early supports and intervention.

1. Introduction

A wide range of adverse neurodevelopmental, sensory, and behavioral outcomes have been documented among children with prenatal alcohol exposure (PAE) (Astley, 2010; Astley et al., 2009; Carr et al., 2010; Subramoney et al., 2018). Fetal alcohol spectrum disorders (FASD), an umbrella term representing the full range of physical, cognitive, and behavioral impairments caused by PAE, are estimated to occur in at least 1% of children and youth in the general population (Popova et al., 2019; Roozen et al., 2016). Children with PAE and FASD are a clinically heterogenous group, who may experience brain-based challenges across multiple domains including cognition, language, executive function, motor, self-regulation, and adaptive behavior functioning (Astley, 2010; Mattson et al., 2019). Although earlier diagnosis provides opportunities for children to benefit more fully from intervention and is predictive of more positive life outcomes in this population (Streissguth et al., 2004), PAE appears to be under-recognized by early childhood practitioners. In fact, many referrals for FASD diagnosis are not initiated until a child reaches school age (Olson et al., 2007), well beyond the time for early intervention. Challenges related to effective screening processes for maternal alcohol use history, as well as difficulties detecting early signs of delays or problems in the absence of physical features, may be inhibiting the early identification and intervention of infants/toddlers with PAE (Clarren & Astley, 1998; Olson et al., 2007; Watson et al., 2011).

Understanding the early neurodevelopmental effects among infants/toddlers with PAE is necessary to facilitate early diagnosis and intervention, a top priority in the field of FASD (SAMSHA, 2014). Decades of research has documented the developmental outcomes of infants/toddlers with PAE, frequently relying on global, standardized measures such as the Bayley Scales of Infant Development (Bayley, 1993; 2006; for a review of literature see (Garrison et al., 2019; Subramoney et al., 2018). Many of these earlier studies used the Bayley-II (Bayley, 1993), for example, which provides a general indication of functioning when it combines cognitive, expressive, and receptive language outcomes into one index (i.e., Mental Developmental Index) and gross and fine motor development into a second index (i.e., Pyschomotor Developmental Index). Given that young children with PAE show considerable individual variability in development (Astley, 2010; Astley et al., 2009), more useful information may be generated from a developmental profile that examines outcomes across distinct scales. Other global measures of infant/toddler development, including newer versions of the Bayley (Bayley et al. (2019); Bayley (2006), are comprised of distinct domains and/or subdomains, which broadens the scope of the assessment. Furthermore, assessment of infant/toddlers' functioning in each of the five core developmental domains (i.e., cognitive, language, motor, social-emotional and adaptive functioning), for the purpose of identifying suspected delays and determining early intervention eligibility, is consistent with federal (Yell et al., 2006) and professional early childhood (Zeanah et al., 2016) standards.

Impairments in self-regulation have been frequently observed in young children (birth to 8 years) with PAE (Astley, 2010; Reid & Petrenko, 2018) and as such, have been recognized as a core symptom in the FASD 4-Digit Code diagnostic criteria for "Neurobehavioral Disorder/Alcohol-Exposed and the proposed DSM-5 diagnostic criteria for "neurobehavioral disorder associated with PAE (ND-PAE)" (Kable et al., 2016). Self-regulation is defined as the ability to manage internal sensory, emotional, and behavioral states (Wells et al., 2012). These are the skills that allow children to regulate and respond to sensory input, pay attention, practice self-control, and manage strong emotions in an adaptive and age-typical manner. Sensory processing refers to an individual's capacity to detect, modulate, interpret, and respond to everyday sensations (Dunn, 2007; Miller et al., 2007). As such, information about early regulatory skills, which may be reflected in sensory processing behaviors and emotional and behavioral functioning, helps to broaden the picture of overall child development.

Documenting self-regulatory difficulties is important both for understanding the variable developmental performance of infants/toddlers with PAE and for guiding intervention. Caregiver rating scales and questionnaires have frequently been used to assess sensory processing differences and emotional/behavioral problems in the early childhood period (Astley, 2004, 2010; Coles et al., 2015; Fjeldsted & Xue, 2019; Molteno et al., 2014). Findings from a recent comparative analysis demonstrate the usefulness of caregiver-reported assessments for identifying behavioral deficits in infants with PAE, including those with light/moderate PAE (Bakhireva et al., 2018). However, for children older than three, researchers suggest that both caregiver-reported observations/ratings and performance-based measures of neurodevelopment be included to establish a comprehensive profile of FASD (Astley & Clarren, 2000; Lange et al., 2017). Taken together, findings underscore the importance of collecting relevant information from multiple sources to accurately identify developmental and behavioral problems across a continuum of infants/toddlers at risk for FASD (Astley, 2013).

This study aimed to explore the prevalence of neurodevelopmental delay, atypical sensory processing, and emotional and behavioral problems in a clinical sample of infants/toddlers with confirmed PAE to assist early childhood practitioners in identifying

early delays or problems that may arise from PAE. Given that alcohol is a neurobehavioral teratogen and children with PAE often experience high levels of co-occurring postnatal risks, outcomes were also explored in relation to PAE and selected demographic and environmental factors (Hemingway et al., 2020). The following research questions were asked:

1. What is the prevalence of neurodevelopmental delay in five core developmental domains (i.e., cognitive, language, motor, social-emotional and adaptive behavior)?
2. What is the prevalence of atypical sensory processing behaviors among infants/toddlers with PAE?
3. What is the prevalence of emotional and behavioral problems among infants/toddlers with PAE?
4. Are these adverse outcomes positively correlated with PAE and/or other postnatal risk factors? Does the prevalence of adverse outcomes differ by gender and age?

2. Methods

2.1. Research design

This study is a retrospective exploratory analysis of clinical data obtained from 125 infant/toddlers, ages 2–42 months, who received an interdisciplinary FASD diagnostic evaluation at the University of Washington Fetal Alcohol Syndrome Diagnostic and Prevention Network (FASDPN) clinic between 2009 and 2019. Children were referred to the clinic if they had a confirmed prenatal alcohol exposure history, at any level. Referral to the FASDPN does not require evidence of developmental delay. Data used for this study were collected with University of Washington Human Subjects Division oversight and approval and caregiver consent at the time of diagnosis.

The clinic has provided FASD diagnostic evaluations for individuals of all ages with PAE since 1993 and is one of the few clinics nationally that diagnose children under the age of three. The FASDPN database currently contains over 2000 fields of data (exposures and outcomes) on approximately 3000 patients (newborn to adult) with PAE. All patients in the FASDPN database received an FASD diagnostic evaluation by an interdisciplinary team (medical doctor, occupational therapist, psychologist, and speech language pathologist) using the FASD *4-Digit Diagnostic Code* (Astley, 2004, 2013). The 4 digits of the code reflect the magnitude of expression of the 4 key diagnostic features of FASD in the following order: (1) growth deficiency, (2) FAS facial features, (3) central nervous system (CNS) structural, neurological and/or functional abnormality, and (4) prenatal alcohol exposure. The magnitude of expression of each feature is ranked independently on a 4-point Likert scale with 1 reflecting complete absence of the FASD feature and 4 reflecting strong

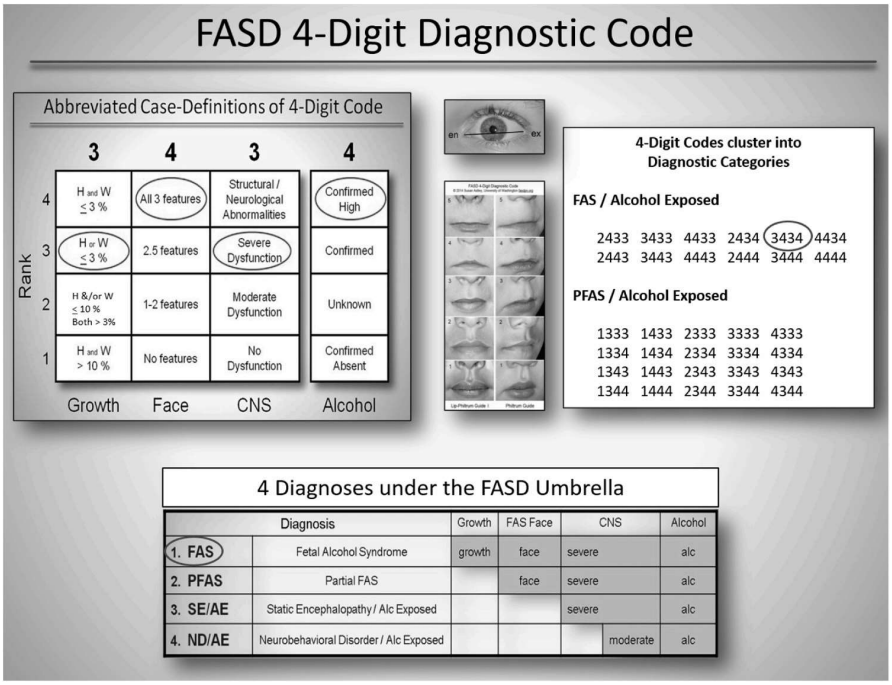


Fig. 1. Abbreviated case-definitions of the FASD 4-Digit Code (Astley, 2004, 2013). The 4-Digit Code 3434 is one of 12 Codes that fall under the diagnostic category FAS. The 4-Digit Code produces four diagnostic subgroups under the umbrella of FASD: FAS, PFAS, SE/AE and ND/AE. Abbreviations: Alc alcohol; CNS central nervous system; h height; w weight; % percentile.

"classic" presence of the FASD feature. Each Likert rank is specifically case defined (Fig. 1). There are 102 4-Digit codes that fall broadly under the umbrella of FASD. These codes cluster into four clinically meaningful FASD diagnostic subcategories (Astley, 2004): Fetal Alcohol Syndrome (FAS) (diagnostic categories A, B); Partial FAS (PFAS) (diagnostic category C); Static Encephalopathy/Alcohol Exposed (SE/AE) (diagnostic categories E, F) and Neurobehavioral Disorder/Alcohol Exposed (ND/AE) (diagnostic categories G, H). Not all individuals with PAE present with adverse outcomes that meet criteria for FASD. The FASD 4-Digit Code classifies these individuals as follows: "Sentinel Physical Findings/Alcohol-Exposed" (SPF/AE) (diagnostic category I; individuals with PAE who present with growth and/or facial abnormalities, but normal CNS outcomes) and "No Physical Findings or CNS Abnormalities/Alcohol-Exposed" (Normal/AE) (diagnostic category J). See Fig. 1. The FASD 4-Digit Code also ranks the magnitude other prenatal risks (e.g., other teratogens, illicit drugs, tobacco, poor prenatal care, family genetics) and postnatal risks (e.g., neglect, trauma, multiple home placements).

2.2. Participants

Data from children who met the following inclusion criteria were used in this study: 1) age 1 month to 3.5 years at the time of their FASD diagnostic evaluation; 2) received one of the following diagnoses FAS, PFAS, SE/AE and ND/AE, SPF/AE, Normal/AE reflecting the full continuum of outcomes observed among individuals with PAE using the FASD 4 Digit Diagnostic code; 3) had complete data on a minimum of two domains from the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III; Bayley, 2006); and D) were of any race, ethnicity, or gender. The upper age range of the inclusion criteria was based on the age range of the Bayley Scales of Infant Development.

2.3. Measures and methods of data collection

The data used for this study were collected by an interdisciplinary diagnostic team using the FASD 4-Digit Code (Astley, 2004). While a core set of assessments are used during the diagnostic clinic visit, the final battery of assessments administered to each infant/toddler are based on clinician judgement. Therefore, data may be limited by clinically warranted situations and decisions where testing was not appropriate or not completed (e.g., child had a recent comprehensive assessment from another provider, or child was unable to attend to items, or child became irritable, upset or tired). Thus, complete data for outcomes on the Bayley-III from this clinical sample vary based on factors such as age, presenting developmental concern(s), and child's ability to complete the assessment. Standardized parent questionnaires were completed by the primary caregiver prior to the scheduled diagnostic clinic date. Time, effort, or other demands placed on a caregiver may have resulted in some caregiver-report measures not being fully completed.

2.3.1. Child and family demographics

Information about child demographics, birth and medical history, growth, prenatal and postnatal experiences was collected during the intake process and caregiver interview at the time of diagnosis.

2.3.2. Assessment of infant/toddler development across five domains

Infants/toddlers were clinically assessed by the occupational therapist using the Bayley-III, a widely used, standardized developmental assessment for infants/toddlers, 1–42 months of age. The Bayley-III has five domains (i.e., Cognitive, Language, Motor, Social-Emotional, and Adaptive Behavior) that are presented as standard scores (mean = 100, *SD* = 15). Each of the five domains has 1–10 subdomains that are presented as scaled scores (mean = 10, *SD* = 3). Three of the domain scales are performance-based measures (i.e., Cognitive, Language, and Motor) and two scales are caregiver-report measures (i.e., Social-Emotional and Adaptive Behavior). For this study, domain and subdomain scores were collapsed into the following categories: domain scores: typical development (standard scores $\geq$ 86, scores ≥ -0.9 *SD*), at-risk development (78–85, scores between -1.0 and -1.4 *SD*), and delayed development ($\leq$ 77, scores ≤ -1.5 *SD*); subdomain scores: typical development (scaled scores $\geq$ 8, scores ≥ -0.9 *SD*), at-risk development (6–7, scores between -1.0 and -1.4 SD), and delayed development ($\leq$ 5, scores ≤ -1.5 SD). These categories were created to reflect current eligibility criteria for early intervention services in the state of WA. The Bayley-III is reported to have high internal consistency demonstrated by Cronbach's alphas, ranging from .91 to .93 for domain scores and .86 to .91 for scaled scores (Albers & Grieve, 2007).

2.3.3. Assessment of sensory processing

The Infant Toddler Sensory Profile (ITSP; 7–36 months; (Dunn, 2002) is a 48-item caregiver-report questionnaire designed to measure sensory processing abilities in children ages 7–36 months. Caregivers rate the frequency of their child's daily behavior on a scale from "*almost always"* (score of 1) to *"almost never"* (score of 5). Sensory processing was evaluated across five sections (i.e., auditory, visual, tactile, vestibular, and oral sensory processing). Infants/toddlers also received a score on their behavioral responses to sensation within four quadrants: low registration (i.e., fails to notice and respond to sensory input), sensation seeking (i.e., derives pleasure from and seeks out sensory experiences), sensory sensitivity (i.e., notice sensory input easily, tends to be reactive) and sensation avoiding (i.e., notices sensory input easily, tends to withdraw quickly). The ITSP categorizes the raw scores as typical performance (scores at or between plus 1.0 *SD and minus 1.0 SD*), probable differences (scores within -1.1 to -1.9 SDs or $+1.0$ to $+1.9$ SDs) and definite difference (scores at or below -2 SDs or at or above $+2$ SDs). The ITSP is reported to have excellent test-retest reliability ($\alpha = .86$) for domain/section scores and adequate ($\alpha = .74$) for quadrant scores (Eeles et al., 2013). Validity was established in several studies (Dunn, 2002; Dunn & Daniels, 2002; Eeles et al., 2013).

2.3.4. Assessment of emotional and behavioral problems

The Child Behavior Checklist for ages 1½– 5 years (CBCL; (Achenbach & Rescorla, 2000) is a widely used instrument used to identify a range of behavioral and emotional problems in young children. Completed by the primary caregiver, the CBCL contains 100 items, rated as 0 = not true, 1 = sometimes true, and 2 = very true or often true, based on the preceding 2 months. The CBCL yields scores on three summary scales (Internalizing, Externalizing, and Total Problems), seven syndromes (Emotionally Reactive, Anxious/Depressed, Somatic Complaints, Withdrawn, Sleep Problems, Attention Problems, and Aggressive Behavior), and five DSM-oriented scales (Affective, Anxiety, Pervasive Developmental, Attention Deficit/ Hyperactive and Oppositional Defiant Problems). Summary scale *t*-scores are categorized as normal range (*t*-scores < 60), borderline clinical range (*t*-scores 60 to 63), and clinical range (*t*-scores ≥ 64). Syndrome and DSM-oriented *t*-scores are categorized as normal range (*t*-scores ≤ 64), borderline clinical range (*t*-scores 65 to 69), and clinical range (*t*-scores ≥ 70). This measure is reported to have high levels of internal consistency (α = 0.97) and good test–retest reliability (mean *r of.85* across all scales) (Rescorla, 2005).

2.3.5. Diagnostic outcome data

FASD 4-Digit Code Diagnoses. FAS; PFAS; SE/AE; ND/AE; Sentinel Physical Findings/AE; No Physical or CNS Abnormalities/AE. See full description above (Astley, 2004) and case definitions for the following diagnostic features (Fig. 1).

Growth Deficiency. 'Growth Rank': 1 = none; 2 = mild; 3 = moderate; 4 = severe. This variable yields the first digit in the FASD 4-Digit Diagnostic Code and documents the magnitude of prenatal and/or postnatal growth deficiency (Astley, 2004).

FAS Facial Phenotype. 'Face Rank': 1 = absent; 2 = mild; 3 = moderate; 4 = severe. This variable represents the second digit in the FASD 4-Digit Diagnostic Code and documents the magnitude of expression of FAS facial phenotype defined by short palpebral fissure lengths, a smooth philtrum, and a thin upper lip using the FAS Facial Photographic Analysis Software (Astley, 2004; Astley, 2016).

CNS Likelihood of Structural Abnormality. 'CNS Rank': 1 =unlikely; 2 =possible; 3 =probable;4 =definite. This variable yields the third digit in the FASD 4-Digit Diagnostic Code. These four ranks document the increasing likelihood of CNS structural abnormality. Alcohol is a teratogen that interferes with the structural development of the fetal brain. This, in turn, can lead to abnormal function. The greater the dysfunction, the higher the probability of CNS structural abnormality (Astley et al., 2009; Astley et al., 2009; Astley, 2013). The first three CNS Ranks document the severity of CNS dysfunction (Rank 1-no dysfunction; Rank 2- mild-to-moderate dysfunction; Rank 3-severe dysfunction). CNS Ranks 1–3 are based on brain function (executive function, memory, cognition, social/adaptive skills, academic achievement, language, motor, attention, and activity level) assessed by an interdisciplinary team using standardized psychometric tools. CNS Rank 4 documents the presence of direct evidence of CNS structural and/or neurological abnormalities (e.g., microcephaly, structural brain abnormalities, a seizure disorder of prenatal origin, or other hard neurological signs).

Prenatal Alcohol Exposure. 'Alcohol Rank': 1 = confirmed absence of exposure; 2 = unknown exposure; 3 = confirmed exposure; level unknown or low to moderate; 4 = confirmed exposure; level high). Alcohol exposure is the fourth digit in the FASD 4-Digit Diagnostic Code, which is ranked according to the quantity, timing, frequency, and certainty of exposure during pregnancy. A confirmed prenatal alcohol exposure at any level is required for a diagnostic evaluation in the FASDPN clinic. The clinic intake form (New Patient Information Form (Astley, 2004)) requests the following exposure information before and during pregnancy: average and maximum number of drinks per drinking occasion, average number of drinking days per week, trimesters of exposure and source of information. The primary sources of information are past and present medical and social service records. Roughly half of patients with confirmed prenatal alcohol exposure report quantity, frequency and duration of exposure. (see appendix 2 from Astley, 2004, 2013).

2.4. Other risk factors

Other Prenatal Risks. Rank: 1 = no risk; 2 = unknown risk; 3 = some risk; 4 = high risk (Astley, 2004). Other prenatal risk factors documented in the FASDPN clinical database include, but are not limited to poor prenatal care, pregnancy complications, prematurity, presence of other syndromes/genetic abnormalities, and prenatal exposure to other substances (e.g., medications, tobacco, illicit drugs, and/or other teratogens). The 4-Digit Code ranks the magnitude of these other prenatal risks in a single composite measure labeled "Other Prenatal Risks Rank." Rank 4 is assigned when there is exposure to another teratogen (e.g., Dilantin) or when another syndrome or genetic condition is present (e.g., Down syndrome, Fragile X, etc.). Rank 3 is assigned to all other prenatal risks. The clinic intake form requests the patient to report these other prenatal risk factors when known. The ranking is determined by available records and caregiver or other report on intake forms and/or clinical interview (Astley, 2004).

Other Postnatal Risks. Rank: 1 = no risk; 2 = unknown risk; 3 = some risk; and 4 = high risk (Astley, 2004). Postnatal risk factors documented in the FASDPN database include, but are not limited to perinatal complications, number of home placements, physical and/or sexual abuse, neglect, and trauma. The 4-Digit Code ranks the magnitude of these other postnatal risks in a single composite measure labeled "Other Postnatal Risks Rank". Rank 4 is used to note severe postnatal circumstances that have been shown to have a significant adverse effect on development in most instances. Examples include physical or sexual abuse, multiple home placements, and severe neglect. Rank 3 is used to note conditions akin to those in Rank 4, but the circumstances are less severe. The clinic intake form requests the patient to report these other postnatal risk factors when known.

3. Data analysis

Data analyses were completed using SPSS 27.0 (IBM Corp., New York). Descriptive statistics (e.g., means, standard deviations, proportions) were used to summarize the sociodemographic and clinical profiles of the study sample and to describe children's scores

Table 1
Demographic and clinical profiles of infants/toddlers with Bayley-III, ITSP, and CBCL assessments.

	Bayley-III		**ITSP**		**CBCL**	
Characteristic	*n*	(valid %)	*n*	(valid %)	*n*	(valid %)
Total *n*	125		93		67	
Sex						
Female	64	(51.2)	50	(53.8)	39	(58.2)
Male	61	(48.8)	43	(46.2)	28	(41.8)
Age at FASD Diagnostic Evaluation (months)						
Birth to 11	22	(17.6)	9	(9.7)	0	0.0
12 - 23	45	(36.0)	42	(45.2)	18	(26.9)
24 - 35	44	(35.2)	39	(41.9)	36	(53.7)
36 - 42	14	(11.2)	3	(3.2)	13	(19.4)
Mean (SD)	22	(0.84)	22	(0.69)	28	(0.57)
Race/Ethnicity						
White	58	(46.4)	47	(50.5)	33	(49.3)
Black	5	(4.0)	3	(3.2)	2	(3.0)
Native American/Canadian	9	(7.2)	7	(7.5)	5	(7.5)
Hispanic	3	(2.4)	2	(2.2)	0	0.0
Asian	1	(0.8)	0	0.0	0	0.0
Mixed race	50	(40.0)	34	(36.6)	27	(40.3)
4-Digit Code FASD Diagnosis (Diagnostic category)						
FAS (AB)	5	(4.0)	0	0.0	0	0.0
PFAS (C)	5	(4.0)	4	(4.3)	1	(1.5)
SE/AE (EF)	13	(10.4)	8	(8.6)	8	(11.9)
ND/AE (GH)	75	(60.0)	62	(66.7)	41	(61.2)
Sentinel physical findings/AE (I)	5	(4.0)	4	(4.3)	5	(7.5)
No evidence of CNS abnormalities/AE (J)	22	(17.6)	15	(16.1)	12	(17.9)
Growth Rank						
Rank 1	71	(56.8)	54	(58.1)	41	(61.2)
Rank 2	21	(16.8)	15	(16.1)	10	(14.9)
Rank 3	22	(17.6)	20	(21.5)	12	(17.9)
Rank 4	11	(8.8)	4	(4.3)	4	(6.0)
Face Rank						
Rank 1	68	(54.4)	53	(57.0)	38	(56.7)
Rank 2	41	(32.8)	31	(33.3)	24	(35.8)
Rank 3	9	(7.2)	8	(8.6)	4	(6.0)
Rank 4	7	(5.6)	1	(1.1)	1	(1.5)
CNS Rank: Structural Damage Risk						
Rank 1, unlikely	27	(21.6)	19	(20.4)	17	(25.4)
Rank 2, possible	75	(60.0)	62	(66.7)	41	(61.2)
Rank 3, probable	2	(1.6)	8	(8.6)	0	0.0
Rank 4, definite	21	16.8)	1	(1.1)	9	(13.4)
CNS Functional Rank						
Rank 1, no dysfunction	29	(23.2)	20	(21.5)	18	(26.9)
Rank 2, moderate dysfunction	81	(72.8)	72	(77.4)	48	(71.6)
Rank 3, severe dysfunction	5	(4.0)	1	(1.1)	1	(1.5)
Prenatal Alcohol Exposure: Alcohol Rank						
3. Confirmed exposure: Amount moderate or unknown	55	(44.0)	43	(46.2)	31	(46.3)
4. Confirmed exposure: Amount high	70	(56.0)	50	(53.8)	36	(53.7)
Other Prenatal Risks: Rank						
1. No risk	1	(0.8)	0	0.0	0	0.0
2. Unknown risk	1	(0.8)	1	(1.1)	1	(1.5)
3. Some risk	121	(97.6)	91	(98.9)	66	(98.5)
4. High risk	1	(0.8)	0	0.0	0	0.0
Postnatal Risk: Rank						
1. No risk	11	(8.8)	9	(9.7)	4	(6.0)
2. Unknown risk	1	(0.8)	1	(1.1)	1	(1.5)
3. Some risk	75	(60.0)	55	(59.1)	36	(53.7)
4. High risk	38	(30.4)	28	(30.1)	26	(38.8)

(*continued on next page*)

Table 1 (*continued*)

	Bayley-III		ITSP		CBCL	
Number of Home Placements						
One	39	(31.2)	29	(31.2)	23	(34.3)
Two	44	(35.2)	35	(37.6)	26	(38.8)
Three to ten	42	(33.6)	29	(31.2)	18	(26.9)
Caregiver at Diagnosis						
Biological mother	39	(31.2)	28	(30.1)	15	(22.4)
Biological father	3	(2.4)	0	0.0	2	(3.0)
Other biological family member	28	(22.4)	23	(24.7)	16	(23.9)
Foster parent	45	(36.0)	35	(37.6)	26	(38.8)
Adoptive parent	7	(5.6)	4	(4.3)	6	(9.0)
Other/caseworker	3	(2.4)	2	(2.2)	2	(3.0)

Notes: fetal alcohol spectrum disorder (FASD); fetal alcohol syndrome (FAS); partial FAS (PFAS); static encephalopathy/alcohol exposed (SE/AE); neurobehavioral disorder/alcohol exposed (ND/AE); occipital-frontal circumference (OFC).

on measures of neurodevelopment, sensory processing, and emotional and behavioral problems (Research Questions 1–3). Associations between Bayley-III, ITSP and CBCL outcomes and selected child demographics and exposures (age, gender, PAE and postnatal risk factors) were examined using chi-squared tests (χ^2), *t*-tests or one-way analysis of variance (ANOVA), as appropriate (Research Question 4). Results having an alpha level of $p \leq .05$ (two-tailed) were considered statistically significant. No adjustments were made for multiple comparisons due to the exploratory nature of this study; thus, significant findings should be interpreted accordingly.

With regard to missing data, any subject with complete data on two or more Bayley-III domains and the entire CBCL were included in the analyses. For the ITSP, any subjects with missing data on more than one-third of items in any one quadrant/section were excluded. On the rare occurrences (n = 8) when less than a third of items were missing, the average of the child's remaining scores was calculated and rounded to the nearest whole number. This value replaced the missing score(s) in that quadrant/section.

4. Results

4.1. Demographic and clinical outcomes

Records from 125 infants/toddlers with PAE met the inclusion/exclusion criteria for this study. All 125 had a Bayley-III administered. Sixty-one (49%) infants/toddlers had all five domains on the Bayley-III completed; 27 (22%) had 4 domains; 31 (25%) had 3

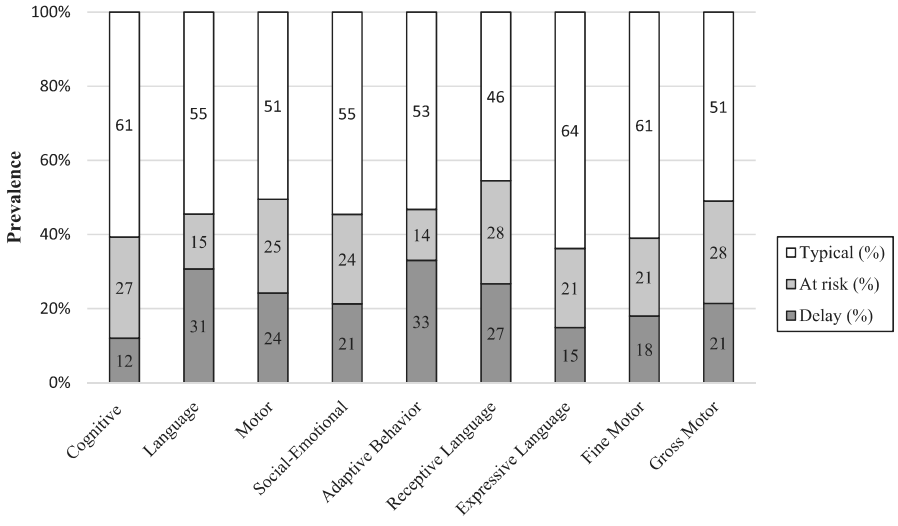


Fig. 2. Proportion of 125 infants/toddlers with typical, at-risk, and delayed development across the five Bayley-III domains: typical (standard scores ≥ 86, scores ≥ −0.9 *SD*); at-risk (78–85, scores between −1.0 and −1.4 *SD*); delayed (≤ 77, scores ≤ −1.5 *SD*) and proportion of infants/toddlers with typical, at-risk, or delayed development in the Bayley-III Language and Motor subdomains. Receptive language: n = 90, expressive language: n = 94, fine motor: n = 100, and gross motor: n = 98. Typical (scores ≥ −0.9 *SD*). At-risk (scores between −1.0 and −1.4 *SD*). Delayed (scores ≤ −1.5 *SD*).

domains; and 6 (5%) had 2 domains. ITSP outcomes were available for 93 of the 125 infant/toddlers and CBCL outcomes were available on 67 infant/toddlers. The full sample of 125 ranged in age from 0.28 to 3.5 years (mean = 1.9 years), was 51% female and 46% white (Table 1). Diagnostic outcomes spanned the full continuum of FASD, with a majority of these young children receiving a diagnosis of ND/AE (60%). An overwhelming majority of our sample (90–98%) had documented exposure to prenatal and/or postnatal risks, in addition to their PAE. At the time of the assessment, 34% percent of infants/toddlers were living with their birth mother or father. The demographic and clinical profiles of the current study sample were largely representative of the entire birth to 3.5-year population evaluated in the FASDPN clinic ($n = 468$) from which they were drawn. The demographic and clinical profiles of infants/toddlers with Bayley-III, ITSP, and CBCL assessments were comparable to one another.

4.2. Research Question 1: Developmental performance on the Bayley-III

Bayley-III outcomes are presented in Figs. 2 and 3. The proportion of infants/toddlers that presented with delayed development (≤ -1.5 *SDs*) within each of the five domains ranged from Cognitive (12%), Social-Emotional (21%), Motor (24%), Language (31%), and Adaptive Behavior (33%). Within the Language and Adaptive Behavior domains, the most prevalent delays were observed in Receptive Language (27%) and Adaptive Behavior's Self Care (44%).

Of the 61 infants/toddlers with complete data across all five domains, 53 (87%) had one or more domains or subdomains with a developmental delay. Of the 125 infants/toddlers with two or more domains assessed using the Bayley-III, 93 (74%) had one or more domains or subdomains with a developmental delay. Since not all domains were assessed, 74% serves as a minimal estimate.

4.3. Research question 2: Sensory processing performance on the ITSP

Ninety-three infants/toddlers ranging in age from 7–36 months had a completed ITSP. Compared to the larger group of 125 children with Bayley-III assessments, this subgroup had no infants/toddlers diagnosed with FAS. The distribution of Bayley-III domain scores by classification category (typical, at-risk, delayed) in this subgroup was, however, very similar to the distribution of Bayley-III domain scores in the full group of 125 infants/toddlers. This would suggest the subgroup of 93 was likely reasonably representative of the full study group of 125.

Within each quadrant and section of the ITSP, roughly half of the infant/toddlers presented with outcomes in the probable or definite difference range (Fig. 4), with two exceptions (i.e., sensory seeking and visual processing). The most prevalent atypical patterns observed were Low Registration (reflecting a high threshold for sensory input and use of passive strategies to respond) and Auditory Processing (reflecting an inadequate ability to modulate sounds representing over or under responsiveness). Of the 93 infants/toddlers who completed the ITSP, all were rated with a definite difference in at least one quadrant/section of the ITSP.

4.4. Research question 3: Emotional and behavioral functioning on the CBCL

Sixty-seven infants/toddlers ranging in age from 18–42 months had a completed CBCL assessment. Compared to the larger group of

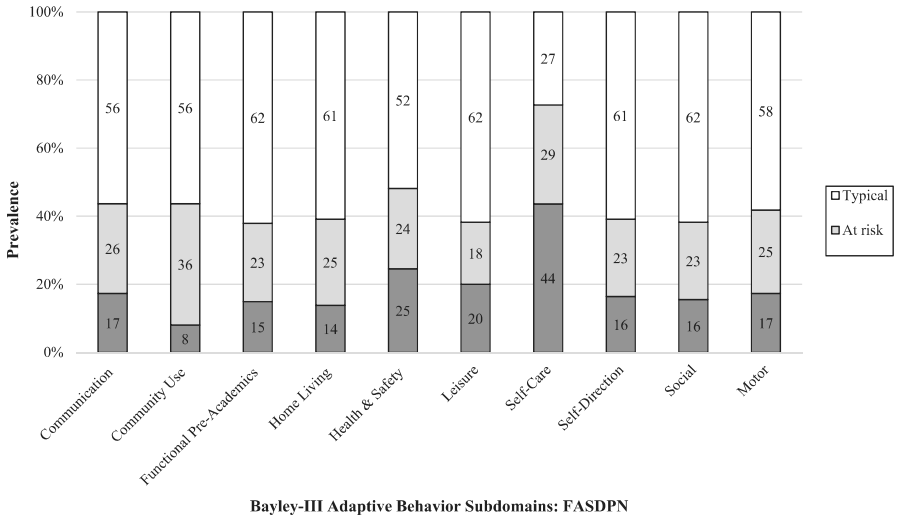


Fig. 3. Proportion of infants/toddlers with typical, at-risk, or delayed development in the Bayley-III Adaptive Behavior subdomains. Communication: n = 110, community use: n = 87, functional pre-academics: n = 87, home living: n = 87, health & safety: n = 110, leisure: n = 110, self-care: n = 110, self-direction: n = 110, social: n = 110, and motor: n = 110. Typical (scores ≥ -0.9 *SD*). At-risk (scores between -1.0 and -1.4 *SD*). Delayed (scores ≤ -1.5 *SD*).

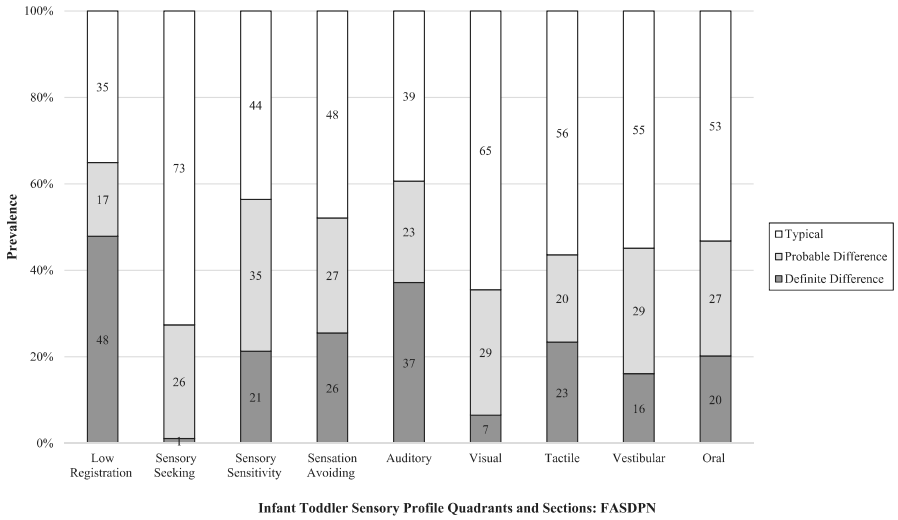


Fig. 4. Proportion of 93 infants/toddlers with typical performance, probable difference, or definite difference across the four ITSP quadrants (low registration, sensory seeking, sensory sensitivity, sensory avoiding) and five section (auditory, visual, tactile, vestibular, and oral sensory processing). Typical performance (scores at or between plus 1.0 *SD and minus 1.0 SD*), probable difference (scores within −1.1 to −1.9 SDs or within +1.0 to + 1.9 SDs), and definite difference (scores at or below −2 SDs or at or above +2 SDs).

125 infants/toddlers, this subgroup had no children diagnosed with FAS and only one child with PFAS. The distribution of Bayley-III domain scores by classification category (typical, at-risk, delayed) in this subgroup was comparable to the full group of 125 infants/toddlers.

Approximately half of the infants/toddlers presented in the borderline or clinical range on the Internalizing, Externalizing and/or Total problem scales (Fig. 5). Attention Problems had the highest prevalence of elevated scores on the Syndrome scales (37%) and Pervasive Developmental Problems had the highest prevalence of elevated scores on the DSM-Oriented Scales (42%; Fig. 5). Of the 67

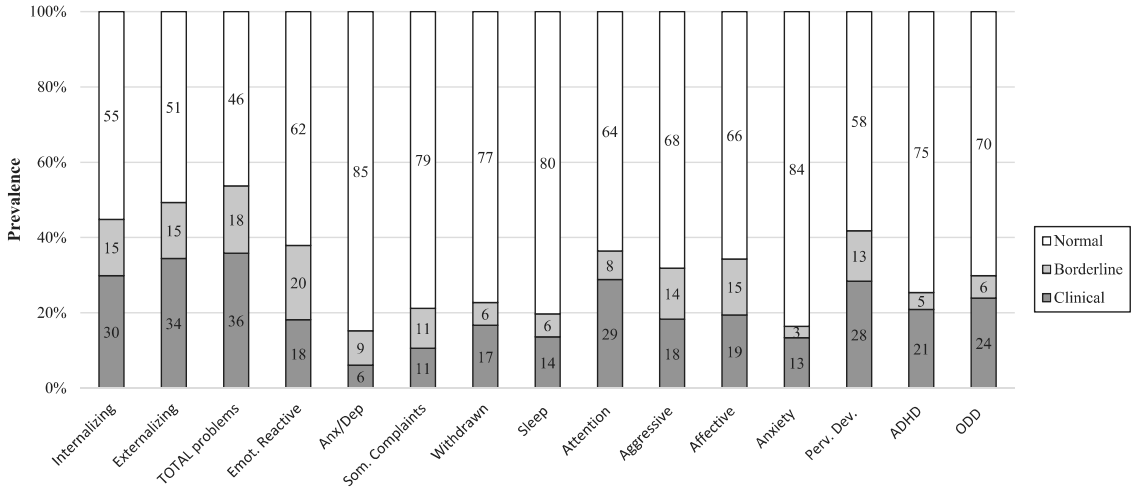
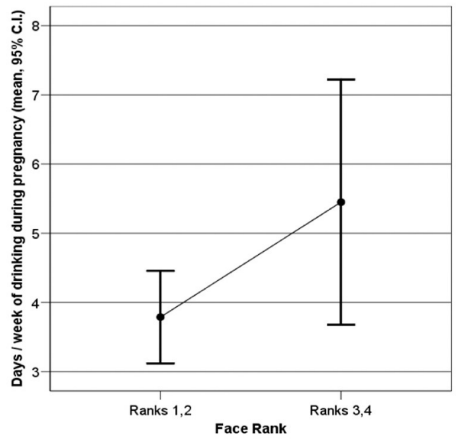
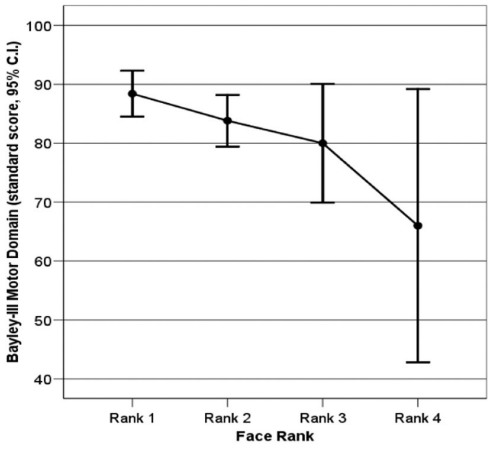


Fig. 5. Proportion of 67 infants/toddlers with scores in the normal, borderline clinical and clinical range across three Summary Scales (Internalizing, Externalizing and Total problems), seven Syndrome Scales (Emotionally Reactive, Anxious/Depressed, Somatic Complaints, Withdrawn, Sleep, Attention, and Aggressive problems) and five DSM-Oriented Scales (Affective, Anxiety, Pervasive Developmental, Attention Deficit Hyperactivity, and Oppositional Defiant problems) of the CBCL. Summary *t*-scores are categorized as Normal (*t*-scores < 60), Borderline (*t*-scores 60 *to* 63) and Clinical (*t*-scores ≥ 64). Syndrome and DSM-Oriented Scale *t*-scores are categorized as Normal (*t*-scores ≤ 64), Borderline (*t*-scores 65 *to* 69), and Clinical (*t*-scores ≥ 70).

A.



B.



C

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Fig. 6. Mean scores across all Bayley-III domains and subdomains (with the exception of Adaptive Behavior) decreased with increasing PAE. Using the Motor domain as an example: A. The mean Bayley-III Motor score decreased with increasing number of days/week of drinking during pregnancy ($t = 0.9$, $p = 0.36$). Only 60 infants/toddlers had days/week of exposure reported, limiting the statistical power to identify significant outcomes. B. Face Rank is a proxy measure for PAE and was available on all 125 infants/toddlers. Infants/toddlers with Face Ranks 3 and 4 had significantly higher days/week of PAE than infants/toddlers with Face Ranks 1 and 2 ($t = -2.0$, $p = .05$). C. Using Face Rank as a proxy measure for PAE, mean Bayley-III Motor scores decreased significantly with increasing Face Rank (ANOVA F linear term 14.3, $p = .000$). Mean scores across all Bayley-II domains decreased with increasing PAE.

infant/toddlers with CBCL data, 29 (43%) scored in the clinical range on the Internalizing, Externalizing and/or Total Problem scales.

4.5. Outcomes spanning all three measures

Two additional exploratory analyses were conducted to document the proportion of infants/toddlers who presented with a clinically significant delay (≤ -1.5 *SDs*) in one or more areas of the Bayley-III, ITSP and CBCL. Of the 31 infants/toddlers with full data across all three assessments, 30 (97%) presented with a clinically significant delay in at least one area of the Bayley-III, ITSP and/or CBCL, while 17 (55%) presented with a clinically significant delay across all three assessments. For the entire sample of 125 infants/toddlers (including those with complete and incomplete data), 124 (99%) presented with a clinically significant delay in at least one area of the Bayley-III, ITSP and/or CBCL.

4.6. Research Question 4: Associations between independent variables (PAE, other postnatal risk factors, gender and age) and dependent variables (Bayley-III, ITSP, CBCL)

Mean scores across all Bayley-III domains and subdomains (with the exception of the Adaptive Behavior domain) were lower (although not significantly lower) among those infants with 5–7 days/week of PAE compared to those with 1–4 days/week of PAE (Fig. 6A). Decades of analyses conducted with FASDPN data has shown that the greater the number of days/week of drinking during pregnancy (i.e., 5–7 days/week versus 1–4 days/week), the more severe the FAS Facial Rank (Astley, 2010, 2013). Only 62 infants had days/week PAE reported, limiting the statistical power to identify significant associations. Previous research has confirmed the FAS Facial Rank serves as an accurate proxy measure of PAE. Data from the first 1400 patients diagnosed at the WA FASDPN document the more severe the 4-Digit FAS facial phenotype (Facial Ranks 1–4), the greater the number of days/week of drinking during pregnancy (significant linear trend, F=10.7, $p = 0.001$) (see Figure 10 from Astley, 2013). Since this same association was observed in the current study (Fig. 6B), the FAS facial rank was used as a proxy for PAE in the current study. Unlike the limited number of infants/toddlers with days/week of PAE reported, all 125 infants/toddlers had a Facial Rank. All Bayley-III domain and subdomain scores (with the exception of Adaptive Behavior) decreased significantly with increasing severity of the FAS facial phenotype (as demonstrated in Fig. 6C for the Motor domain). Domain standard scores decreased roughly 10–20 points from Face Rank 1 to Face Rank 4. Subdomain

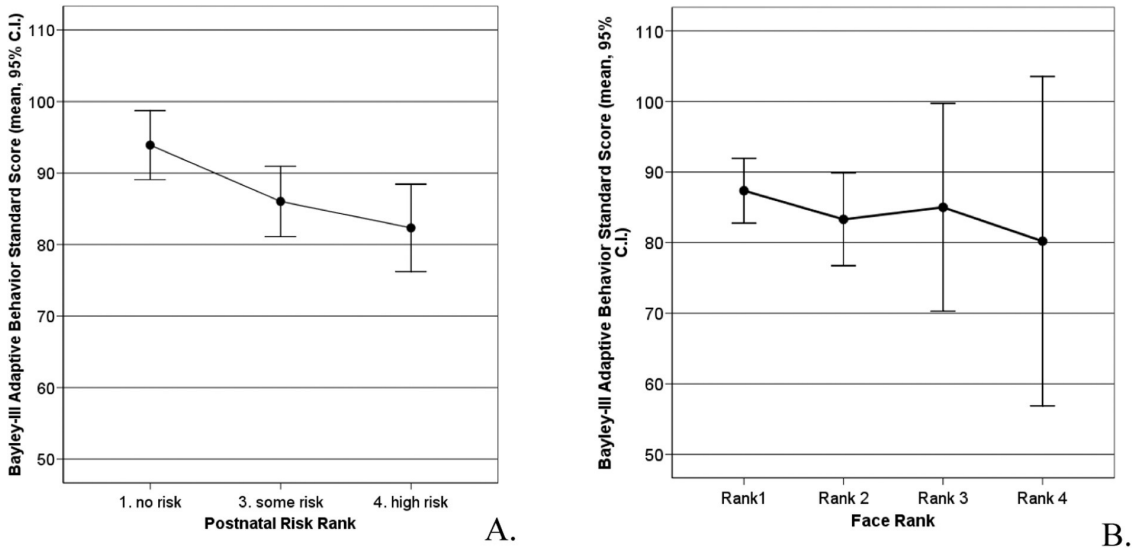

Fig. 7. Impairment in Adaptive Behavior appeared to be more strongly associated with postnatal risk factors than PAE. A. The mean Bayley-III Adaptive Behavior standard score decreased approaching statistical significance with increasing severity of the postnatal risk rank (Linear Term: $F = 1.7$, $p = 0.067$). B. The mean Bayley-III Adaptive Behavior standard score did not decrease linearly with Face Rank (a proxy measure for PAE) (Linear Term: $F = 0.6$, $p = 0.46$).

scaled scores decreased roughly 2–4 points from Face Rank 1 to Face Rank 4. Fig. 7.

The magnitude of postnatal risk was also explored with outcomes across the Bayley-III domains. Interestingly, the mean scores in the Adaptive Behavior domain decreased with increasing levels of postnatal risk, and approached significance (ANOVA: $F = 3.4$, $p = .067$). This is in contrast to mean scores in the other developmental domains whereby scores decreased relative to PAE, but not for the postnatal risk rank. The number of home placements, as a proxy measure of postnatal risk, were also explored relative to Bayley-III outcomes. Mean Cognitive and Expressive Language scores were significantly inversely correlated with the number of home placements ($r = -.18$, $p = .049$ and $r = -.21$, $p = .041$, respectively).

To explore developmental competencies across the early intervention years, two age categories were created (2–23 months and 24–42 months). Limited sample sizes precluded the use of four age categories (i.e., one for each year of life). Delays in the Language and Motor domains were significantly more prevalent (45% vs 10%, $X^2 = 12.8$, $p = .002$% and 35% vs 11%, $X^2 = 8.3$, $p = .016$ respectively) among the younger age group (2–23 months) than the older age group (24–42 months). Conversely, Social-Emotional delays were significantly more prevalent among the older age group relative to the younger group (28% vs 15%, $X^2 = 6.0$, $p = .049$). Mean Language domain scores (89, *SD* 13.9) were significantly higher among females than males (83.2, *SD* 13.3) ($t = -2.0$, $p = .048$).

Limited sample sizes precluded in-depth analyses of three ITSP quadrants/sections because they were divided into multiple age categories (i.e., Sensation Seeking, Tactile and Oral Sensory processing). However, for those remaining quadrants/sections without multiple age categories (i.e., Low Registration, Sensory Sensitivity, Sensation Avoiding, Auditory, Visual and Vestibular processing), no significant associations were found for age, gender, PAE, postnatal risk, and number of home placements.

The prevalence of emotional and behavioral problems did not vary significantly by age, gender, PAE, or number of home placements. However, scores on the Withdrawn and Oppositional Defiant Problems scales were positively correlated with increasing level of postnatal risk rank ($r = .25$, $p = .048$ and $r = .28$, $p = .024$ respectively).

5. Discussion

This research is notable as it is the first paper to describe a wide range of developmental, sensory, and behavioral outcomes in a very young sample of children with confirmed PAE from a specialty clinic for individuals with PAE. Of the 31 infants/toddlers with full data across all three assessments, 30 (97%) presented with a clinically significant delay in one or more areas of the Bayley-III, ITSP and/or CBCL, while 17 (55%) presented with one or more clinically significant delays in each of the three assessments. For the entire sample of 125 infants/toddlers (including those with complete and incomplete data), 124 (99%) presented with a clinically significant delay in one or more areas of the Bayley-III, ITSP and/or CBCL. These findings highlight the substantial diversity and prevalence of challenges experienced by infants/toddlers with PAE during the early intervention period.

5.1. Developmental outcomes and implications

Within each of the five Bayley-III domains, roughly half the infant/toddler study population had at-risk or delayed development. The prevalence of delayed development was lowest in the Cognitive (12%) and Motor (24%) domains, higher in the Language domain (31%) and highest in the Adaptive Behavior domain (33%). This pattern of delayed development was remarkably comparable to the pattern observed among the first 1400 patients with PAE (infant to adult) evaluated in the FASDPN clinic through 2005 (Astley, 2010) and among the 2283 patients with PAE evaluated at the FASDPN through 2020 (infant to adult) presented on the FASDPN Tableau Dashboard (Hemingway, 2022a). While the pattern of developmental delay (from least prevalent to most prevalent) is comparable between this infant/toddler study sample and our predominantly older childhood/adult FASD clinical population, the prevalence of severe impairment (2 or more SDs below the mean) in each domain is roughly two-fold greater in the older childhood/adult population (cognition 24%, motor 25%, language 39%, adaptive behavior 59%) (Hemingway, 2022a). Given that older children and adults have more mature neuropsychological function and can be assessed with more sophisticated neuropsychological instruments, one might expect to detect a higher prevalence of impairment when using these more sensitive instruments (Clarren et al., 2000). These findings provide evidence that a global developmental measure, such as the Bayley-III, may be useful for identifying early indicators of delay among infants/toddlers with PAE. Early identification leads to early intervention. A future longitudinal study is planned to assess whether the Bayley-III predicts which individual infant/toddlers go on to present with cognitive, language, motor, social emotional and/or adaptive behavior impairments later in childhood.

In this clinical sample of infants/toddlers, significant correlations were observed between PAE and developmental delay. Findings demonstrated that Bayley-III domain and subdomain scores (with the exception of Adaptive Behavior) decreased significantly with increasing levels of PAE, which further supports known trends on the gradient effect of alcohol on severity of outcomes (Astley, 2013; Carr et al., 2010; Subramoney et al., 2018). Individuals with PAE typically present with a multitude of other prenatal and postnatal risk factors that likely contribute, at least in part, to their adverse outcomes. Hemingway et al. (2020) reported other prenatal and postnatal risk factors were 3 to 7-fold more prevalent in the FASDPN clinical population than in the general population. Ninety percent of this infant/toddler population presented with adverse prenatal and postnatal risks. Significant correlations were observed between postnatal risks including multiple home placements and adaptive behavior, cognition, and expressive language delays. Similar to literature showing associations between early adverse experiences and poorer functioning in the general population (Garner & Shonkoff, 2012; van der Kolk, 2003), and among individuals with PAE (Coggins et al., 2007; Hemingway et al., 2020; Price et al., 2017; Streissguth et al., 2004), our analyses revealed a significant correlation between other postnatal risks and adaptive behavior delays. This suggests that the postnatal environment may have an impact on these developing behaviors, warranting further research since

adaptive behaviors are a lifelong disability and because there continue to be ongoing questions about the impact of biological vs environmental risks in this complex population of children.

5.2. Sensory processing outcomes and implications

Atypical sensory processing behaviors were observed in a large proportion of infants/toddlers. Based on our work with older children with PAE (Jirikowic et al., 2020; McLaughlin et al., 2019), the sensory processing patterns most impacted were low registration (65%) and auditory processing (61%). In general, infants/toddlers in this study had a high threshold for sensory input (e.g., does not notice stimuli easily) and used passive strategies to regulate (e.g., remains in situations that are uncomfortable rather than controlling for the amount and type of input). Infants/toddlers also showed a decreased capacity to modulate sound, as evidenced by ratings of over-responsiveness or under-responsiveness to auditory input. Definite differences in low registration and auditory processing were similarly reported in a clinic-referred sample of infants/toddlers with PAE, with even more severe impacts in those diagnosed with FASD (Fjeldsted & Xue, 2019). Current findings were consistent with those using FASDPN clinical data (Jirikowic et al., 2020; McLaughlin et al., 2019), showing that preschool and school-age children with FASD had the highest proportions of definite differences in Auditory Filtering and Under-responsive/Sensation Seeking domains using the Short Sensory Profile (SSP; McIntosh et al., 1999). Although an exact comparison cannot be made between ITSP and SSP domain categories, findings suggest that a caregiver-reported measure of sensory processing, such as the ITSP, may be useful for identifying sensory processing differences among infants/toddlers with PAE. Importantly, a child's ability to engage and participate successfully in everyday life, including forming healthy attachment relationships, is closely tied to their sensory processing abilities (Dunn, 2007). When early intervention providers and families have a working knowledge of sensory processing, they can reframe their understanding of their child's behavior and develop appropriate intervention strategies.

5.3. Emotional and behavioral functioning outcomes and implications

Atypical emotional and behavioral problems on the CBCL were observed in a large proportion of infants/toddlers. Results are consistent with prior research demonstrating that problem behaviors co-occur in older children with FASD (Astley, 2010; Astley et al., 2009; Franklin et al., 2008; Jirikowic et al., 2008). Notably, the prevalence of Total Problem scores in the clinical range for the older children (5–10 years of age) (86%; Franklin et al., 2008) and 79% among 997 children 6–18 years of age from the FASDPN clinic (Hemingway, 2022b) were much higher in comparison to the current sample of infants/toddlers (birth to3.5 years of age) with PAE (36%). The prevalence of Attention Problems in the clinical range (61% among 730 children 6–18 years of age from the FASDPN clinic (Hemingway, 2022b) was 3-fold greater than the prevalence (21%) among the infant/toddlers in the current study. A future longitudinal study, with larger numbers and a comparison group, would add significantly to the literature on the trajectory of emotional and behavioral outcomes in young children with PAE and the protective and risk factors associated with these outcomes.

5.4. Limitations

This study had a number of potential limitations. First, because this was a retrospective chart review using diagnostic clinical data, our results are limited by the clinical data available. Missing data due to a flexible clinical assessment protocol and some incomplete caregiver-report measures contributed to uneven datasets for each infant/toddler, thus limiting the analysis of outcomes at the individual level. Future studies, with a larger prospective sample and assessments spanning similar age ranges, could examine neurodevelopmental profiles in relation to sensory processing differences and problem behavior. Additionally, further research could examine how factors such as attachment relationships, family engagement or early intervention impact infant/toddlers' emerging, and declining competencies. Second, this was a clinic-referred sample and might not represent all infants/toddlers with PAE. It is important to note that the FASDPN clinic does not require patients to present with a concern or delay in order to receive an FASD evaluation; they only need to have a confirmed PAE at any level. For this reason, our study sample may more closely resemble the broader population of infants/toddlers with PAE compared with other clinic-referred samples. Third, the ITSP, CBCL and Adaptive Behavior components of the Bayley-III are standardized measures based on caregiver report, which are inherently susceptible to reporting bias. Nevertheless, researchers working towards the earlier identification of children with PAE (Astley, 2010; Bakhireva et al., 2018), and children with autism spectrum disorders (Zwaigenbaum & Maguire, 2019), advocate for the use of caregiver-reported assessment to identify early appearing problems in development and behavior. One additional limiting factor to consider is the potential for cohort effects, given that data from this sample of infants/toddlers were collected over a 10-year time span (2009–2019). No annual temporal trends were observed from 2009 to 2019 across any of the following study population characteristics: number of infant/toddlers diagnosed, gender, race, FASD diagnostic outcome or level/rank of prenatal alcohol exposure.

6. Conclusion

An overwhelming majority of infants/toddlers with PAE in this sample presented with clinically significant delays in development, sensory processing and/or emotional and behavioral functioning. Present findings, considered with similar studies reported in the literature, suggest that most domains of child functioning are vulnerable to the teratogenic impact of PAE and that these delays are evident in the first years of life. Findings reinforce the value of early screening, ongoing monitoring, and comprehensive assessment to facilitate earlier identification and to provide opportunities for infants/toddlers with PAE and their caregivers to benefit more fully

from early supports and intervention.

CRediT authorship contribution statement

Jirikowic Tracy: Conceptualization, Formal analysis, Supervision, Writing – original draft, Writing – review & editing. **Pruner Misty:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Astley Hemingway Susan J.:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Baylor Carolyn:** Conceptualization, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

None

Data Availability

The data that has been used is confidential.

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Washington State
Fetal Alcohol Syndrome Diagnostic & Prevention Network (FASDPN)

29th Annual Report

Summary of Progress from July 1 1995 through June 30 2024

www.fasdpn.org
www.fasdwa.org

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UW FASDPN website www.fasdpn.org

WA State FASD website www.fasdwa.org

FAS DPN FAS Diagnostic & Prevention Network

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What is FASD?

Fetal alcohol syndrome (FAS) is a permanent birth defect syndrome caused by maternal consumption of alcohol during pregnancy. FAS is characterized by growth deficiency, permanent brain damage, and unique facial features. Not all children exposed to alcohol during gestation are born with FAS. Many are born with the same severity of brain damage, but do not have the facial features that permit a diagnosis of FAS. These children need the same social, educational, and healthcare services as children with FAS and far outnumber children with FAS. The full spectrum of damage caused by prenatal alcohol exposure is called Fetal Alcohol Spectrum Disorders (FASD). For every child with FAS, there are 10 with FASD.

What is the Fiscal Impact of FASD on Washington State?

- It costs WA an estimated 2 million dollars in lifetime social and health care services for every child born with FASD.
- It costs Medicaid 9 time more to cover the medical expenditures for a child with FAS than for a child without FAS.
- Preventing FASD in just one child will pay for over 5 years of the FASDPN operating costs.
- Prevention starts with diagnosis. Women at highest risk for producing children with FASD are women who have already given birth to a child with FASD. The FASDPN clinic identifies over 100 high-risk women annually through the diagnosis of their children.
- It costs Washington State 30 times more to raise a child with FASD than to prevent FASD in a child.
- Published empirical data confirms FASD prevention efforts are working in WA State and FASD diagnoses lead to effective intervention.

VII. FASD Facts

- FASD is 100% preventable. The FASDPN has empirical evidence documenting it is successfully preventing FASD in WA.
- FASD is the leading known cause of intellectual disabilities.
- An estimated 870 children are born with FASD in WA each year (1% of all births).
  An estimated 70,000 individuals with FASD of all ages currently live in WA State.
- FASD is not just a health care issue. Its primary impact is on schools, foster/ adoptive care, the justice system, and mental health services.
- Less than 10% of adults with FASD live independently or remain employed.

What is the WA FAS Diagnostic and Prevention Network (FASDPN)?

- The University of Washington FASD diagnostic clinic opened in 1993. It has been providing FASD diagnostic services for 31 years.
- The clinic expanded into the statewide WA FASDPN in 1995 through RCW 70.96A.500 and is the first program of its kind in the nation.
- The WA FASDPN has included up to 6 Satellite clinics led by the Core diagnostic/research/training site in at the University of Washington. See our interactive data Tableau Dashboards
- The WA State FASDPN is recognized as a national/international model for FASD diagnosis and prevention demonstrating an invaluable partnership between academic research and public health through interagency collaboration (WA FASD Interagency Workgroup).
- Our Mission is FASD prevention through FASD screening, diagnosis, intervention, research, and training.

What does the FASDPN do for children, families, and health care professionals in WA? (2014 FASD State Recommendations)

Diagnostic Program

- The FASDPN provides 100% of the interdisciplinary FASD diagnostic evaluations in WA State. The FASDPN is currently funded to conduct 70 diagnostic evaluations annually. The demand for FASD diagnostic evaluations exceeds the State's current capacity to provide timely FASD diagnostic evaluations. The average wait time for a family seeking an evaluation is 2 to 12 months.
- The FASDPN provides accurate diagnoses and comprehensive care plans for individuals under 22 years of age with prenatal alcohol exposure. Patient satisfaction is high. 92% of families report they received help from us they could not receive elsewhere. 89% report the FASD diagnosis afforded them access to interventions that met their needs. 99% would recommend our diagnostic services to other families in similar need.
- We developed the evidence-based FASD 4-Digit Code Diagnostic System and FAS Facial Recognition Software that is used worldwide.

Training Program

- We provide FASD training to 1000s of community health care, educational, correctional, and social service students and providers statewide.

Screening Program

- We used our FAS Facial Recognition Software to screen all children entering King County Foster Care for FAS for 10 years. The prevalence of FAS in King County foster care is 10 times higher (1/100) than in the general population (1/1000). Early accurate diagnosis is confirmed to reduce secondary disabilities like school failure, job loss, and trouble with the law.

Intervention Services

- Patients/families report tremendous access to and benefit from interventions recommended by the FASDPN clinics. FASDPN published research confirmed early diagnosis and a stable, nurturing home environment led to significantly reduced brain dysfunction. The FASDPN has attracted millions of dollars in free assessment (e.g., MRIs, neuropsychological exams) and intervention services (e.g., 9-month in-home intervention) for hundreds of WA children through the FASDPN research program. Family advocacy is provided by FASD Focus NW.org .

Primary Prevention Program

- We identify women at highest risk to give birth to children damaged by prenatal alcohol, namely the birth mothers of children diagnosed with FASD at our FASDPN clinics. We provide the women with referrals to appropriate community-based programs including the Parent-Child Assistance Program to help them reduce their use of alcohol during pregnancy and practice effective family planning.
- Published evidence supports WA FASD prevention efforts are working! A significant reduction in maternal drinking during pregnancy correlated with a significant reduction in the number of children being born with FAS in WA State.

Research Program

- The FASDPN has attracted millions of research dollars to WA State to support free neuropsychological evaluations, MRIs, and 9-month, in-home intervention services for children and families impacted by FASD (Families Moving Forward).

Executive Summary

The mission of the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network (FASDPN) since its inception in 1993 is primary and secondary prevention of fetal alcohol spectrum disorders (FASD) through screening, diagnosis, intervention, research, and training/education. Primary prevention refers to prevention of FASD births. Secondary prevention refers to prevention of secondary disabilities among individuals exposed to and damaged by prenatal alcohol exposure. The FASDPN's innovation and utility have been nationally and internationally recognized and replicated. A summary of our accomplishments to date is presented in our Legislative Fact Sheet above and detailed in full below.

Washington is one of very few states that has significantly reduced the prevalence of drinking among pregnant women through primary prevention efforts such as those conducted by the FASDPN and the WA State Parent-Child Assistance Program (P-CAP). Women in Washington State reported a significant decrease in their consumption of alcohol during pregnancy from 7.8 percent in 1993 to 3.9 percent in 1998, exceeding the Health People 2010 National Goal of 6% (Washington State DOH, May 2002). This significant decline in the prevalence of maternal drinking during pregnancy corresponded to a significant decline in the prevalence of FAS among foster children born between 1993 to 1998. These observations strongly support that FAS prevention efforts in Washington State were working (Astley, 2004). A comprehensive summary of WA State efforts to prevent FASD from 1968-2004 are posted on the WA FASD website in a document entitled FASD: WA State History.

It is paramount that WA State sustain its successful efforts to reduce the incidence of FASD. Unfortunately, the most recent CDC Pregnancy Risk Assessment Monitoring System (PRAMS) data for WA documents a small, but steady increase in maternal reporting of drinking during pregnancy, in contrast to the steady decline observed in the early 1990s (Astley Hemingway et al., 2023). Preliminary data documents this increase in drinking is associated with an increase in prevalence of FAS in foster care among children born after 1998. To reverse this trend, the WA FAS Interagency Workgroup intensified its efforts on FASD identification, prevention, intervention, and policy as outlined in House Bill 2737. The WA FAS Interagency Workgroup, chaired by Susan Astley Hemingway, PhD, submitted a comprehensive report entitled "Recommendations from the WA FASD IAWG" to the State Legislature in December 2014 to describe the impact of FASD on WA State; identify evidence-based practices for early screening, diagnosis, prevention, and intervention; and recommend policy changes. In 2024 the WA State Legislature approved House Bill 1168 to once again expand diagnostic services and increase availability of intervention.

2024 marks the 32nd year of operation for the University of Washington FASDPN core clinical/research/training clinic and the 29th year of legislative support for the expansion of the UW clinic into a statewide network of FASD clinics (FASDPN). We are gratified with our successes in the last three decades and are appreciative of the continued support we receive from the Washington State Legislature and Division of Behavioral Health and Recovery. This annual report summarizes our activities and progress through June 30, 2024. Essentially all tasks that were proposed to be completed by this date are completed; all work planned to be ongoing at this time is ongoing. The remainder of this report provides further detail on the background and establishment of the FASDPN and our accomplishments to date.

Full Report

I. What is Fetal Alcohol Spectrum Disorder (FASD)?

FASD is an umbrella term used to describe the spectrum of adverse outcomes that can occur in an individual whose mother drank alcohol during pregnancy. These outcomes may include physical and neuropsychological abnormalities with lifelong implications. The term FASD was not intended for use as a clinical diagnosis. Rather, the spectrum of diagnoses that fall under the umbrella of FASD include FAS, Static Encephalopathy/Alcohol-Exposed, and Neurodevelopmental Disorder/Alcohol-Exposed. FAS is a permanent birth defect syndrome characterized by growth deficiency, a unique cluster of minor facial anomalies and structural, neurological and/or functional brain abnormalities. FAS was first discovered by Christy Ulleland, MD at the University of Washington in 1972 (Ulleland et al., 1972). The term FAS was first coined in the medical literature in 1973 by University of Washington professors Kenneth Jones MD and David Smith MD (Jones & Smith, 1973). FASD is the leading known cause of intellectual disability and is 100% preventable. The incidence of FAS is estimated to be 1 to 3 per 1,000 live births in the general population, similar to the incidence of down syndrome (Abel & Sokol, 1987). The prevalence of FAS in King County foster care is 10 times greater than in the general population or approximately 1 out of every 100 children (Astley, et al., 2002). In Washington State an estimated 200 infants are born with full FAS each year. Not all infants exposed to and damaged by prenatal alcohol exposure have FAS. Many infants damaged by prenatal alcohol exposure have brain damage that can be as severe as the damage seen in infants with FAS, but do not have the physical anomalies (growth deficiency and/or facial anomalies) that permit a diagnosis of FAS. The medical, educational, and social service needs of these individuals with Static Encephalopathy/Alcohol Exposed and Neurodevelopmental Disorder/Alcohol Exposed are no different than those with FAS (Jirikowic et al, 2010). In Washington State, an estimated 870 children are born with FASD each year (1% of births) and approximately 70,000 individuals with FASD of all ages currently live in Washington State. Early diagnosis, intervention and a stable, nurturing home environment with intervention and accommodations helps reduce the prevalence of secondary disabilities such as school failure, unemployment, and trouble with the law. This was confirmed in a publication (Astley, 2010) summarizing the outcome of the first 1,400 patients diagnosed at the FASDPN clinics. Despite heavy prenatal alcohol exposure, 9.3% of patients evaluated in the clinic present with normal growth and development. The two features that significantly differentiated this small group of children from the much larger group of children that presented with significant cognitive/behavioral impairments was an early diagnosis and a stable, nurturing home environment.

II. Establishment of and Funding History for the FAS Diagnostic and Prevention Network (FASDPN)

Fetal Alcohol Spectrum Disorder (FASD) has been identified as an important health issue. The 1994 Washington State Public Health Improvement Plan identified maternal substance abuse during pregnancy and the resulting alcohol related birth defects as an important public health issue. The March of Dimes Western Washington Chapter Needs Assessment (1992) community Delphi survey found the communities' top concern was perinatal substance abuse and its resultant problems. The Washington State 1995 MCH Title X Block Grant identified substance use/abuse during pregnancy and its resultant negative outcomes as an area of focus for 1995. In 1992, Congress mandated the CDC to lead national efforts in FASD prevention. In response to the mandate, the CDC released an Request of Proposals that would fund 5 clinical research teams nationwide to empirically assess proposed methods for FASD prevention. The University of Washington was one of the five recipients of the CDC funding. The UW proposed to identify and intervene with women at highest risk for bearing

children with FAS/D by opening the first ever interdisciplinary FASD diagnostic clinic. Women at highest risk for bearing children with FAS/D are women who have already given birth to a child with FAS/D.

Back in 1992, FASD was not easily assigned to any specific medical specialty or governmental agency for overall leadership. Psychiatrists are primarily interested in problems of substance abuse, obstetricians are primarily interested in pregnancy risk reduction, pediatricians and pediatric subspecialties like genetics, dysmorphology, neurology, and developmental disabilities are primarily interested in the diagnosis and management of affected children (it is unclear who has specialty concern for affected adults). All of these groups express interest and some expertise in dealing with a portion of the FASD management problem, but no specialty is positioned to assume responsibility for the whole. Similarly, in government, the challenges faced by these affected individuals requires the involvement of schools, social service agencies, alcohol treatment agencies, the criminal justice system, vocational rehabilitation, developmental disabilities, health agencies, etc. All of these agencies have an important role to play in helping affected patients, but no single agency is in a position to organize and direct services across recognized divisional and departmental boundaries.

Providing diagnostic and intervention services to both mother and child through a FASD Diagnostic Clinic not only benefits the mother and child but has the potential of being a very cost-effective approach to FASD primary prevention (Astley et al., 2000a). Based on the results of the study published by Astley et al., (2000a), one out of every three patients evaluated in the FASDPN clinics is diagnosed with FAS or Static Encephalopathy/Alcohol Exposed. The birth mothers of one out of every three of these children can be directly contacted. Half of the birth mothers directly contacted will still be at risk for producing more children damaged by prenatal alcohol exposure. Thus one out of every 18 children evaluated in the FASDPN clinics has a birth mother who can be found and is at risk for giving birth to more children damaged by prenatal alcohol exposure. The cost to society to raise a child with FAS was estimated to be $1,000,000 in the 1980s (Abel and Sokol, 1987). A diagnostic evaluation for a child through a FASDPN clinic cost approximately $1,200 in 2007 (Astley et al., 2007a). Providing effective intervention to the highest risk birth mothers through the Parent-Child Assistance Program cost an estimated $3,800 per year per woman over three years in 1999 (Grant *et al*., 1999). One out of every 10 children evaluated in the FASDPN clinic is diagnosed with full FAS. If, on average, 18 children must be diagnosed to identify and intervene with one high-risk mother, the approximate cost to find and provide effective intervention services to the birth mother would be $33,000 ($21,600 to diagnose 18 children and $11,400 to provide three years of advocacy services to the mother through the P-CAP program). Thus, the cost of raising a child with FAS would be roughly 30 times the cost of preventing FAS in the child. The benefit to the mothers, their children, and society would be immeasurable.

Establishment of the FASDPN: In 1992 the University of Washington entered into a 5-year Cooperative Agreement with the CDC to conduct a FAS primary prevention study that focused on identifying and profiling the needs of women at high risk for giving birth to children with FAS. To identify the women, the CDC provided funds to establish an interdisciplinary FASD Diagnostic Clinic at the Institute on Human Development and Disability at the University of Washington (UW). This was the first ever interdisciplinary FASD diagnostic clinic in the world. The purpose of the clinic was to identify high-risk women through the diagnosis of their affected children. Although the UW clinic had the capacity to see 160 patients per year, the demand for diagnostic services far exceeded its capacity. In 1995, two additional FASD diagnostic clinics, led by the UW FASD clinic, were established in Federal Way and Everett through support from the Western Washington March of Dimes Birth Defects Foundation (Fig. 1). In 1996, the WA State Legislature through Senate Bill 5688

went one step further and expanded the single UW FASD clinic into a statewide network of six Satellite clinics led by the core clinical/research/training site at the University of Washington. In 2019, a 7th FASDPN site was established in King/Snohomish Counties: the Wonderland Hope Rising FASD diagnostic clinic.

The six Satellite FASDPN clinics were established in Spokane, Yakima, Whitman, Pierce, South King and Snohomish Counties (listed below). The University of Washington core staff provided FASD diagnostic training. A diagnostic manual "Diagnostic Guide for FAS and Related Conditions" (Astley & Clarren 1997, 1999; Astley Hemingway 2004, 2024), standardized diagnostic forms, and neuropsychological and motor-sensory assessment batteries were created to assure consistency and accuracy of diagnosis across all FASDPN sites. A comprehensive set of educational materials was also distributed. All sites were networked via interactive video teleconferencing and a centralized database was established.

Figure 1. Locations of FASDPN clinics between 1993-2024.

A. Core FASDPN Clinical/Research/Training Site:
   1. University of Washington, Institute on Human Development and Disability, Seattle. Susan J. (Astley) Hemingway, Ph.D. Director (1993 to present).

B. Six contracted Satellite FASDPN Sites:
   1. Pierce County: Mary Bridge Children's Hospital, Tacoma (1996-1999).
   2. South King County: Federal Way Public Health Clinic, Federal Way (1995-2004).
   3. Whitman County: Wilson Psychological Services, Pullman. (1997-2007).
   4. Spokane County: Sacred Heart Hospital, Spokane. (1997-2010).
   5. Yakima County: Children's Village, Yakima. (1997-2017).
   6. Snohomish County: Providence Medical Center, Everett. (1995-2017).

C. One noncontracted Satellite FASDPN site opened in 2019.
   1.King County: Wonderland Developmental Center, Hope Rising, Bothell (2019-present).

Overall, the six contracted Satellite FASDPN sites were maintained for an impressive number of years with four of the six open for 16 to 21 years. The primary reason for closure was insufficient funds.

Funding History for the Satellite Clinics: The six Satellite FASDPN clinics were community based and community owned since their inception in 1996. Each Satellite clinic typically conducted 1 or 2 diagnoses per month. Up until 2008, the Satellite clinics never received funding support through the FASDPN-DASA contract. The Satellite FASDPN clinics were supported through a variety of

mechanisms including: in-kind service from local professionals, in-kind space from local medical/public health facilities, fee for service (billing Medicaid and/or private insurance), cost shifting (the psychologist, speech language pathologist, and occupational therapist in a clinic are often 'on loan' one day per month from the local school district); and funds from local philanthropic agencies (e.g., March of Dimes, United Way). The Satellite clinics demonstrated the cost of conducting a single diagnostic evaluation in 2008 was approximately $3,500 in Washington State. This cost included administrative costs and professional fees and was commensurate with the cost of an evaluation in a typical neurodevelopmental clinic. Only a small portion of the cost could be billed to and collected from Medicaid and/or private insurance. Securing the remaining funds continued to be the number one challenge for these regional clinics. Many states have replicated the WA State FASDPN model and have encountered similar funding challenges. Alaska established 12 FASD Diagnostic Clinics in 1998. In a report prepared by the Alaska Mental Health Trust Authority, the average cost of a FASD diagnostic evaluation in Alaska in 2001 was $4,821. Like WA, Alaska demonstrated only $1,076 (22%) could be billed to and collected from Medicaid and/or private insurance. Recognizing that Medicaid and/or insurance alone would not cover the full cost of a diagnosis, Alaska established a FASD Diagnostic Services Provider Agreement in 2005. Qualified Alaska FASD diagnostic clinics received a Provider Agreement payment of $3,000 per diagnostic evaluation to cover the costs not covered by Medicaid/insurance. The Alaska Agreement was shared with the Washington State Legislature in Jan 2008. In 2008, the WA Legislature approved $100,000 to cover the cost of 50 FASD diagnostic evaluations conducted by four FASDPN Satellite clinics (Yakima, Pullman, Spokane, and Everett). These funds helped sustain these 4 clinics for a few more years, but by 2017, all four closed due to insufficient funds. The cost of $2,000 per diagnostic evaluation is reflective of costs 15-20 years ago. The current cost of an FASD diagnostic evaluation in 2024 in WA is roughly $6,500. By 2017, most of the FASDPN Satellite clinics closed due to insufficient funds. In 2024, the Legislature approved WA Second Substitute House Bill 1168 to re-establish FASD diagnostic and intervention services statewide. Establishing FASD diagnostic clinics statewide would provide more equitable access to diagnostic services and shorten the wait time for a diagnostic evaluation.

III. Interagency Collaboration and Personnel

Interagency Collaboration: From 1997 through 2014, the FASDPN met with representatives from NOFAS-WA, FASFRI, FADU, P-CAP, OSPI, MAA, CA, ITEIP, JRA, DOC, DOH, DSHS, DCFS, MCH, and IHS quarterly through the FAS Interagency Work Group (FAS IAWG) as stipulated by Senate Bill 5688. These meetings facilitated the development and implementation of all components of the FASDPN program. FASDPN staff members have also participated as speakers for the annual FASD conferences held by the FAS IAWG in 1999, 2000, 2001, 2005. Starting in 2007, the FAS IAWG merged its annual FASD conference with the ongoing Co-Occurring Disorders Conference. The FASDPN created and maintains WA State's FASD website. In 2015, the focus of the FAS IAWG was House Bill 2737. The FAS IAWG submitted a report entitled "Recommendations from the Washington State Fetal Alcohol Spectrum Disorders (FASD) Interagency Work Group" to the Governor and Legislature in December 2014. As an example of the benefits of working collaboratively with State agencies, in March 2015 DDD posted Management Bulletin D15-012 that expanded eligibility from just FAS to the full spectrum of FASD. The more rigorous, evidence-based method of diagnosis (the FASD 4-Digit Code) paved the way for this expanded DDD eligibility.

Key personnel at the University of Washington FASDPN Core site during the 2023-2024 fiscal year are listed below. Those marked with an * have been with the FASDPN for 15-32 years.

*Susan J. Astley Hemingway, Ph.D. FASDPN Director, Professor of Epidemiology/Pediatrics

*Julie Bledsoe, M.D.	Professor and Pediatrician
*Julian Davies, M.D.	Professor and Pediatrician
*Allison Brooks, Ph.D.	Psychologist
*Erin Olson, PhD.	Professor and Psychologist
*John Thorne, Ph.D, SLP	Professor and Speech/Language Pathologist
Ryan Conley, M.S. SLP	Speech/Language Pathologist from Hope Rising Clinic
*Tracy Jirikowic, Ph.D., OTR/L	Professor of Rehabilitation Medicine and OT
Jennifer Nash, Ph.D. OTR/L	Occupational Therapist
Misty Pruner, Ph.D. OTR/L	Occupational Therapist
*Julie Gelo, B.S.	Family Advocate, Director FASD Focus NW
Sandra McIntire	Program Assistant
*Faye Louie, B.S.	Clinic Coordinator

IV. Mission of the FASDPN

The mission of the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network (FASDPN) is primary and secondary prevention of fetal alcohol spectrum disorders (FASD) through screening, diagnosis, intervention, research, and training/education. The FASDPN has achieved each of these missions as outlined below.

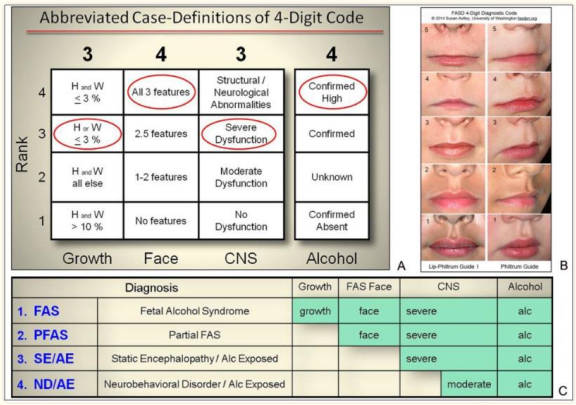
IV.A. Diagnosis

IV.A.1. FASD Diagnostic Model and Method

FASD Diagnostic Model: In 1993, the UW opened the first-ever interdisciplinary FASD diagnostic clinic sponsored by the Center for Disease Control (CDC) as a FASD primary prevention study. Data collected in the clinic was used to develop and validate the FASD 4-Digit Diagnostic Code in 1997 (Astley & Clarren, 1997, 2000). In 2024, the 4th edition of the 4-Digit Code was released (Astley Hemingway, 2024). The 4-Digit Code and interdisciplinary approach to diagnosis is used worldwide.

FASD is characterized by growth deficiency, a unique cluster of 3 minor facial anomalies and structural, neurological and/or functional abnormalities of the brain. Individuals with prenatal alcohol exposure present with a wide range of outcomes, most of which are not specific to (caused only by) prenatal alcohol exposure and often manifest differently across the lifespan. Professionals from multiple disciplines (medicine, psychology, speech-language pathology, occupational therapy) are needed to accurately assess and interpret the broad array of outcomes that define the diagnoses. The pattern and severity of outcome is dependent in part on the timing, frequency, and quantity of alcohol exposure (which is rarely known with any level of accuracy) and the fetus' genetic vulnerability to prenatal alcohol exposure (Astley et al., 2019a). The pattern and severity of outcome is also dependent on the other prenatal and postnatal risk factors that are prevalent among individuals with prenatal alcohol exposure (Astley, 2010; Astley et al., 2020). The FASDPN interdisciplinary team conducts an FASD diagnostic evaluation in one 4-hour evaluation. In preparation for the evaluation, all birth, medical, school and social service records are collected and reviewed. A summary of these records is presented to the team in the first half hour of the diagnostic evaluation. In the next 2 hours, the medical doctor conducts an interview with the caregiver(s) while the psychologist, speech-language pathologist and occupational therapist conduct standardized neuropsychological assessments on the patient. The team reconvenes for one hour and derives the FASD 4-Digit Code and composes a comprehensive intervention recommendation report. In the final half-hour of the evaluation the results are shared with the caregivers and a comprehensive medical summary report is submitted to the patient's medical records.

FASD Diagnostic Method: The FASDPN created the FASD 4-Digit Code in 1997 to guide interdisciplinary teams in the diagnosis of the full spectrum of FASD. A pictorial representation of the FASD 4-Digit Code is presented in Fig. 2). The four digits reflect the magnitude of expression of the four key diagnostic features of FASD in the following order: (1) growth deficiency, (2) the FAS facial phenotype, (3) brain structural, neurological and functional abnormalities, and (4) prenatal alcohol exposure. The magnitude of expression of each feature is ranked independently on a 4-point Likert scale with 1 reflecting complete absence of the FAS feature and 4 reflecting a strong "classic" presence of the FAS feature. Thus, the 4-Digit Code 4444 reflects the most severe expression of FAS (significant growth deficiency, all three FAS facial features, structural/neurological evidence of brain damage, and confirmed prenatal exposure to alcohol). At the opposite end of the scale is the 4-Digit Code 1111 reflecting normal growth, none of the three FAS facial features, no evidence of brain abnormalities, and confirmed absence of prenatal alcohol exposure. Every combination of 4-Digit Code has been observed among individuals with prenatal alcohol exposure evaluated in the WA State FAS Diagnostic & Prevention Network. The 4-Digit Code is fully validated (Astley, 2013) and serves as the cornerstone of a fully integrated and highly successful screening, diagnostic, prevention and surveillance program in Washington State (Astley et al., 2002; Astley, 2004a, 2013; Hemingway (Astley) et al., 2024).



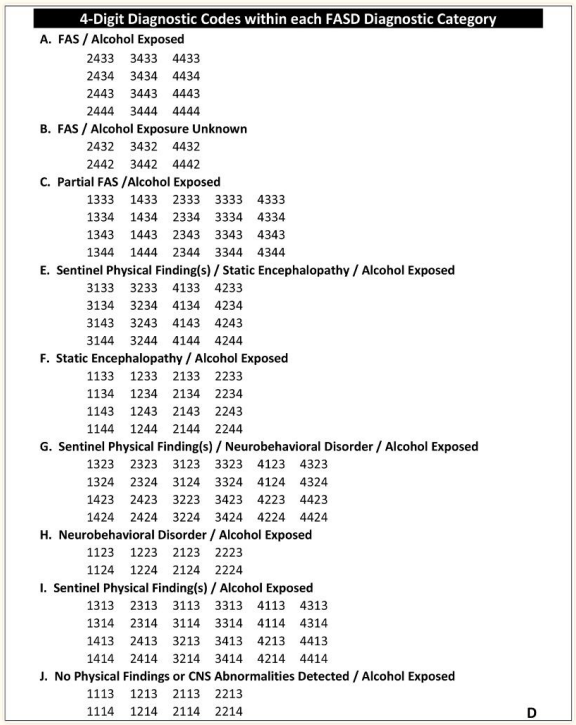


Figure 2. FASD 4-Digit Diagnostic Code.
A) Abbreviated case-definitions for the fetal alcohol spectrum disorder (FASD) 4-Digit Code (Astley, 2004). The 4-Digit Code 3434 is one of 12 4-Digit Codes that fall under the diagnostic category FAS. **B)** The Rank 4 FAS facial phenotype requires 3 features: 1) palpebral fissure lengths 2 or more standard deviations below the mean; 2) a smooth philtrum (Rank 4 or 5 on the University of Washington Lip-Philtrum Guide); and 3) a thin upper lip (Rank 4 or 5 on the University of Washington Lip-Philtrum Guide). **C and D)** The 4-Digit Code produces four diagnostic subgroups under the umbrella of FASD: FAS (Diagnostic Categories A, B), PFAS (Diagnostic Category C), SE/AE (Diagnostic Categories E, F), and ND/AE (Diagnostic Categories G, H). Abbreviations: CNS: central nervous system; H: height percentile; W: weight percentile. The 4-Digit Code was updated in 2024 (Astley Hemingway, 2024)

IV.A.2. FASD Diagnostic Outcomes and Patient Satisfaction

Of the 3,084 patients diagnosed in the FASDPN from 1993 through 2023, 3.3% received a diagnosis of FAS, 4.5% Patial FAS, 26.7% Static Encephalopathy/Alcohol-Exposed and 45.6% Neurodevelopmental Disorder/Alcohol-Exposed (Fig. 3A). The majority of patients were school-aged at the time of their diagnosis with 13.8% birth to 3 years of age and 5.3% 18 years and older (Fig. 3B). More detailed socio-demographics are provided in our profile of the first 1,400 patients diagnosed (Astley, 2010) and via our interactive Tableau Dashboards (e.g., Fig. 4) that are periodically updated. Seventy-eight percent of the patients seen in the FASDPN clinics were no longer in the care of their biological parents. The FASDPN provides accurate diagnoses and comprehensive care plans for individuals under 22 years of age with prenatal alcohol exposure. Ninety-four percent of families report they received medical/educational/social services in our clinics they could not find elsewhere. Ninety-nine percent would recommend the clinic to other families in similar need. Ninety-four percent of families report the intervention services we recommended met some to all their needs (Astley, 2014). A comprehensive profile of the first 1,400 patients evaluated in the WA FASDPN clinics was published in 2010 (Astley, 2010).

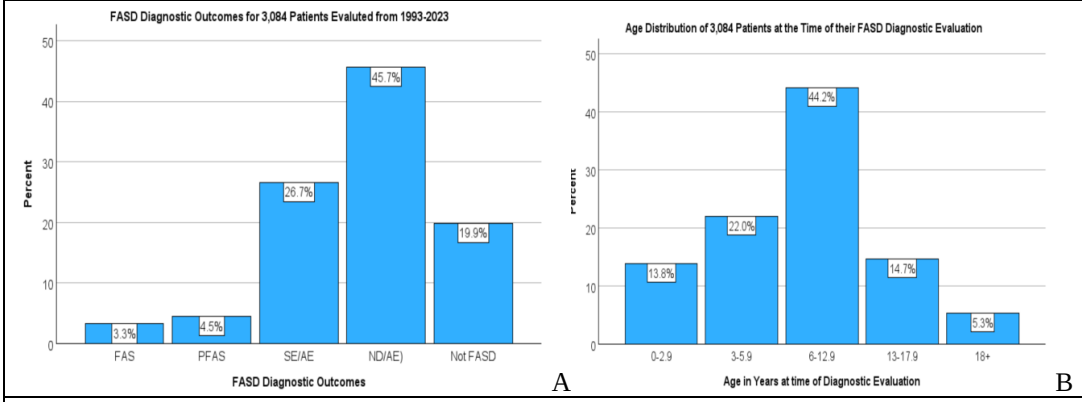


Figure 3. FASD diagnostic outcomes (A) and age distribution (B) of the 3,084 patients diagnosed at the FASDPN clinics from 1993-2023.

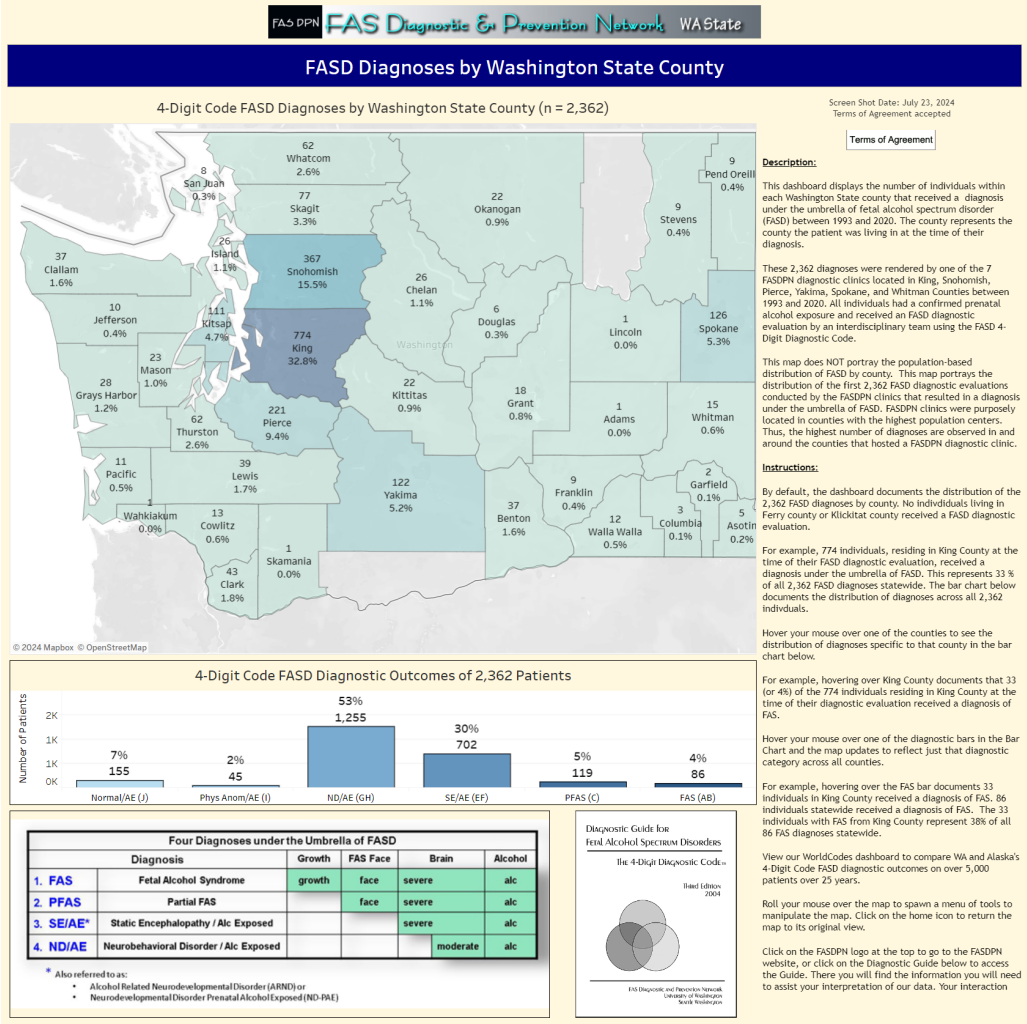


Figure 4. [FASDPN Interactive Tableau Dashboards](#). This interactive dashboard displays the number and percent of individuals receiving a diagnosis under the umbrella of FASD based on the Washington State County they resided in at the time of their FASD diagnostic evaluation. These evaluations were conducted on 2,362 patients between 1993 and 2021. This dashboard is updated periodically

IV.A.3. FASD Diagnostic Demand and Capacity over 30 years

The original University of Washington interdisciplinary FASD Diagnostic Clinic was funded by the CDC from 1993 – 1997 as part of a national FASD prevention study. The CDC-sponsored University of Washington FASD Clinic had the capacity to conduct 160 diagnostic evaluations per year. Patients often had to travel long distances to obtain these FASD diagnostic services in Seattle. In 1995, two additional FASD diagnostic clinics, led by the UW FASD clinic, were established in Federal Way and Everett through support from the Western Washington March of Dimes Birth Defects Foundation. In 1996, one year prior to the completion of the 5-year CDC FAS Prevention Study, funds were received

from WA DSHS, through Senate Bill 5688, to continue support of the University of Washington FASD Diagnostic Clinic and expand it into the Washington State FAS Diagnostic & Prevention Network (FASDPN) through the addition of six Satellite clinics statewide.

Since the opening of the first FASD Diagnostic Clinic at the University of Washington in 1993, the Washington State FASDPN has received 5,473 requests for diagnoses and diagnosed a total of 3,084 patients through 2023, (2,276 (74%) by the University of Washington Clinic and 808 (26%) by the six Satellite Clinics). On average, over the past three decades (1993-2023), the demand for FASD diagnostic evaluations in WA has been roughly twice the diagnostic capacity of the FASDPN clinics. Requests for evaluations are made by submitting a New Patient Information Form (NPIF) (white bars in Figs 4 and 5). An individual is eligible for a FASD diagnostic evaluation if they have a reported prenatal alcohol exposure at any level. Fig. 4 documents the number of NPIFs submitted and FASD diagnoses completed by the patients' county of residence from 1993-2023. The greatest number of requests were received from the largest population centers in WA and correlated with the location of FASDPN clinics over time (e.g., Seattle, Federal Way, Tacoma, Evertt, Pullman, Spokane and Yakima). Fig. 5 documents the number of NPIFs submitted and diagnoses completed annually from 1993-2023. The pattern of requests and diagnoses annually reflects a number of factors that varied across the decades. One important factor was how many clinics were open each year and where they were located. This is portrayed in Fig. 6. In 1993 and 1994, the Seattle clinic at the University of Washington was the first and only FASD diagnostic clinic open in the U.S. (black bars in Fig. 6). Understandably, there was a large backlog of individuals seeking diagnostic evaluations. From 1995 to 2017 additional FASDPN Satellite clinics were opened (depicted by colored bars in Fig. 6), resulting in increased diagnostic demand, capacity and geographic access. The Satellite clinics were community owned and operated and did not receive funding support from the State from 1996 to 2013. The dip in diagnostic activity that occurred in 2008-2009 was due to the national recession that closed the UW FASDPN clinic for 3 months in 2009 and forced the closure of most of the Satellite clinics. It was not until 2013 that the State Legislature allocated funds to help support the Satellite clinics. These funds allowed the Yakima and Evertt clinics to reopen until 2017. By 2018, the UW Core clinic was the only clinic open. The dip in diagnostic demand and capacity in 2019-2022 reflected the impact covid had on the population seeking diagnoses and the UW's ability to safely conduct diagnoses. The UW clinic was closed from March through June of 2020 due to the covid pandemic and reopened in April 2020 using a hybrid zoom/in-person model following covid safety protocols. By 2021 the UW FASDPN clinic was back up to full capacity (70 diagnoses per year). The black bars in Fig. 6 reflect the number of diagnostic evaluations conducted annually by the UW FASDPN core clinic. The number of diagnostic evaluations conducted by the UW FASDPN clinic has varied from 50-160 per year based on funding availability. In 2019, the Hope Rising Clinic in Bothell opened. They provide diagnostic evaluations and intervention for patients with prenatal substance exposure including prenatal alcohol exposure. They were trained to use the FASD 4-Digit Code but have never had a formal contract with HCA or the UW FASDPN, thus have not been in a position to share data with the FASDPN core clinic at the University of Washington.

In fiscal year 2023-24, the only FASDPN clinic open in WA State was at the University of Washington in Seattle. The UW FASDPN clinic was funded to conduct 70 diagnostic evaluations per year. With over 100 patients requesting evaluations, the wait time for some patients was over 1 year. With the closure of the FASDPN satellite clinics in Spokane, Yakima and Pullman by 2017, the number of requests for evaluations from families living in eastern WA decreased considerably, not because the need decreased, but because geographic access to diagnoses decreased. Families impacted by FASD would be better served if FASD diagnostic services were more geographically dispersed and wait times were reduced.

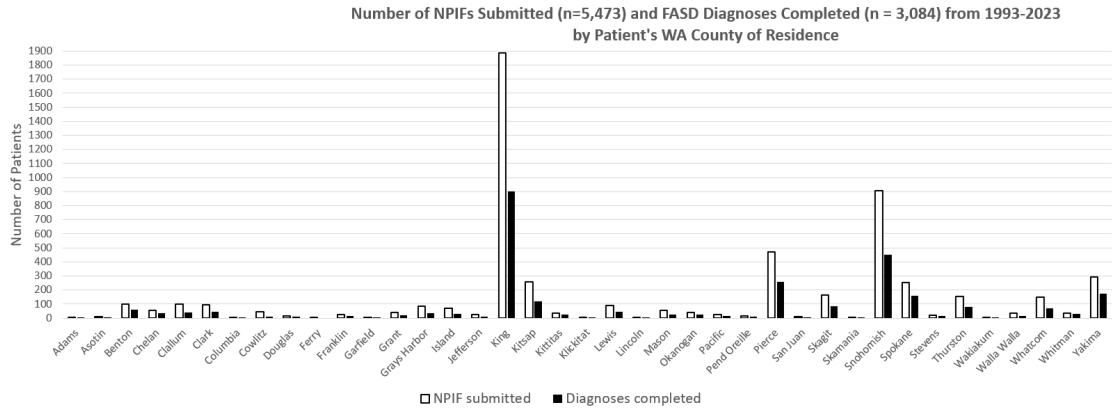


Figure 4. See interpretation of this figure in the text of Section IV.A.3 above.

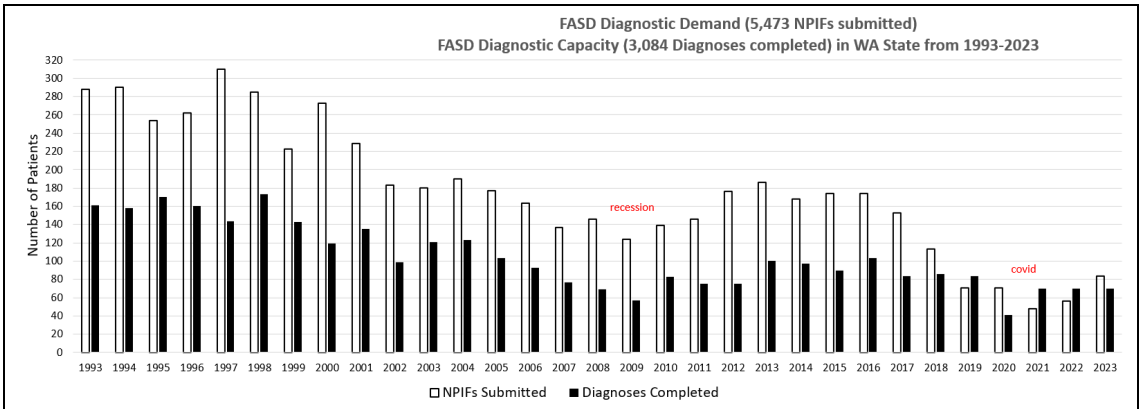


Figure 5. See interpretation of this figure in the text of Section IV.A.3 above.

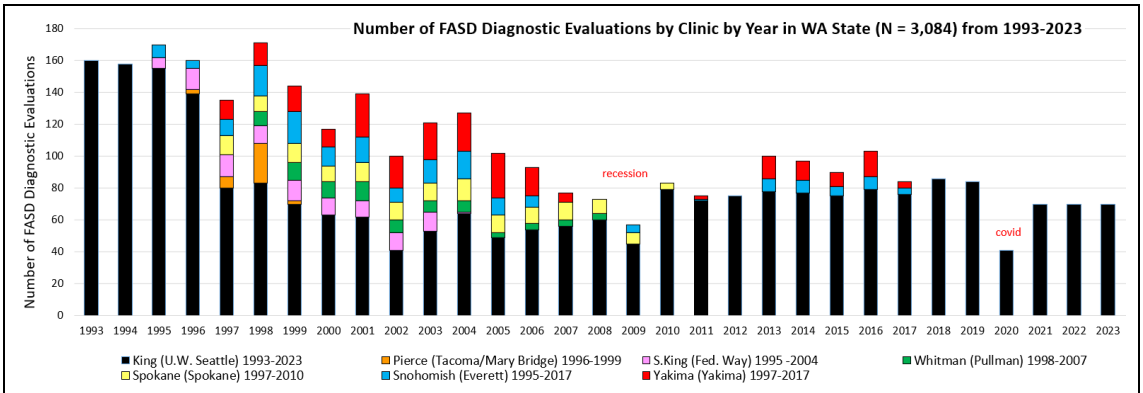


Figure 6. See interpretation of this figure in the text of Section IV.A.3 above.

IV.A.4. Creation and Distribution of FASD Diagnostic Tools and Training Materials

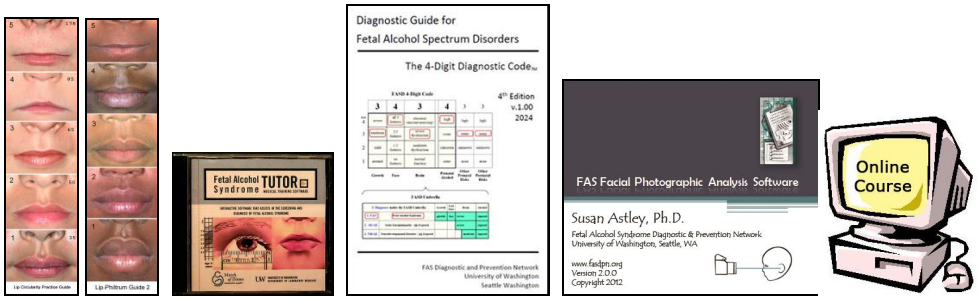


Figure 7. FASD 4-Digit Code diagnostic tools and online training course developed by the FASDPN.

The FASDPN has created and distributes FASD screening, diagnostic and prevention tools and training to a broad array of professionals worldwide (see Fig. 7 and list below). The development of these tools and training materials were supported in part by DSHS and outside contracts. These tools and training materials were developed to assure consistency and accuracy of diagnosis across all FASDPN sites. All are distributed worldwide free of charge.

1. FAS Facial Photographic Analysis Software, 1996, 2003, 2012, 2016.
2. Diagnostic Guide for FASD: The 4-Digit Diagnostic Code, 1st ed. 1997, 2nd ed. 1999, 3rd ed. 2004; 4th edition 2024.
3. FASDPN Clinical Manual, 1997, 1999, 2004
4. Community Development of a FASDPN, 1997, 1999, 2004.
5. FASDPN website (www.fasdpn.org), 1997, updated monthly.
6. Patient/Family Resource Materials and Network Clinical Staff Resource Materials, 1997
7. FASDPN Data Collection and Consent Form Instruction Guide, November 1997.
8. FASDPN Interdisciplinary Clinical Team Training Manual, 1997, 2004.
9. Communicative Behavior Assessment Guide, 1st edition, January 1998.
10. Psychological Assessment and Treatment Planning Manual, 1999.
11. FAS-Tutor™ (an instructional CD-ROM for screening and diagnosing FAS) 1999.
12. Journey through the Healing Circle, 1999.
13. A Child with FAS, In: Handbook of Clinical Assessment for Young Children with Developmental Disabilities, 2000.
14. Intervention Ideas Guide, 2000.
15. Teaching Students with FASD, 2004.
16. FASD 4-Digit Diagnostic Code Online Course, University of Washington, 2005, 2024.
17. Families Moving Forward FASD Intervention Program founded/direct by Heather Carmichael Olson PhD, 2005 to present.
18. Free digital FASD Lip-Philtrum Guides for use on smartphones, 2014.
19. Webinar: Prevention of FASD, 2014, presented by Susan Astley Hemingway, sponsored by Association of Reproductive Health Professionals.
20. Web-based "Talking with Patients about Alcohol Use During Pregnancy Clinical Minutes" 2016 sponsored by Association of Reproductive Health Professionals. Content contributed by Susan Astley Hemingway.
21. FASD: From Discovery to Prevention in WA State 2004 (video presentation) Susan Astley Hemingway PhD.
22. Tableau FASDPN interactive data dashboards.

Dr. Astley Hemingway created the FASD 4-Digit Diagnostic Code for use by interdisciplinary teams back in 1997. It has been updated in 1999, 2004 and 2024. It is a fully validated diagnostic system that is now used worldwide. Thousands of copies of the Guide have been distributed worldwide. Requests have been made to translate the Guide into Russian, German, French, Polish, and Spanish. In 2003, the *FAS Facial Photographic Analysis Software* was created by Dr. Astley Hemingway through funding support from the Washington Research Foundation and as of June, 2024, 3,858 copies of this software have been distributed worldwide. The software is used to screen and diagnose the facial features of FAS. The software was updated in 2012 and 2016 to incorporate new palpebral fissure length normal growth charts. A CD-ROM was developed in 1999 to accompany the FASD Diagnostic Guide. The CD-ROM trained medical professionals to screen and diagnose FASD. The National March of Dimes funded the development of the CD-ROM and has distributed over 3,000 copies nationwide. The National FASD Center for Excellence (2002) described the FASDPN method of diagnosis as a clearly advanced, highly developed approach to diagnosis and screening. Our interdisciplinary approach to diagnosis is regarded as Best Practice worldwide by SAMHSA (2014). In 2015, the American Academy of Pediatrics recognized the WA FASDPN as a national/international leader in FASD. As of February 2024, all diagnostic tools (4-Digit Code Diagnostic Guide (2024), FAS Facial Software (2016), Lip Philtrum Guides (2014) and the 4-Digit Code Online Course (2024) are distributed electronically, worldwide, free of charge.

Dr. Astley Hemingway developed a comprehensive manual entitled "*Diagnostic Guide for FAS and Related Conditions. The 4-Digit Code*" to ensure diagnostic accuracy and precision across all FASDPN clinics. This guide was written in response to the documented lack of accuracy and precision of FAS diagnosis nationwide (Cordero et. al., 1994, Stratton et. al., 1995). The Guide was printed by the University of Washington Publication Services in May 1997. It was distributed by the U.W. FASDPN Core site to all FASDPN personnel free of charge and was sold nationally and internationally at cost. A second edition of the Guide was printed in May 1999 to coincide with the release of the FAS-Tutor CD-ROM. This 2nd edition provides further instruction and clarity on the use of the 4-Digit Diagnostic Code for FAS. A comprehensive summary of the 2nd edition was published in the peer-reviewed medical journal *Alcohol & Alcoholism* in July 2000. A 3rd edition was released in 2004 by Dr. Astley: *Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code*. A 4th edition was released in 2024 by Dr. (Astley) Hemingway. The latest edition is distributed worldwide, free of charge.

FASDPN clinical team members Heather Carmichael Olson, Ph.D., Sandra Clarren, Ph.D., Sharon Beck, M.Ed. and Tracy Jirikowic, M.O.T. finalized the '*Psychological Assessment and Treatment Planning Manual'* based on information gained from conducting comprehensive psychometric evaluations at the U.W. FASDPN Core site in 1998. This final edition was distributed to each of the FASDPN network sites during the FASDPN "Assessing Brain Dysfunction" training in May 1999.

Robin LaDue and Carolyn Hartness authored "Journey Through the Healing Circle", a series of CDs and illustrated workbooks narrated by Native American storyteller Loyd Red Crow Westerman, who uses animal stories to talk about children with FAS and the problems families face with these effects. Funded by the WA DSHS. The series showcases the UW FASDPN clinic and interdisciplinary approach to FASD diagnosis.

Funds were received from the National March of Dimes Birth Defects Foundation to create a compact disk to instruct physicians on how to screen and diagnose FAS using the tools and manuals developed by the FASDPN. This CD entitled *FAS-Tutor™* was created through a collaborative effort between Dr. Astley Hemingway at the U.W. FASDPN and Dr. Astion in the Department of Laboratory Medicine at the University of Washington. This CD was distributed nationwide by the National March of Dimes.

FASDPN clinical team members Sandra Clarren, Ph.D. (psychologist) and Tracy Jirikowic, Ph.D. (occupational therapist) created the "*Intervention Ideas Guide, 2000*" based on information gained from conducting comprehensive psychometric evaluations at the U.W. FASDPN Core site and the collective experiences of parents and professionals who have worked with or raised children with prenatal alcohol exposure. This reference guide was distributed to each of the FASDPN network sites during the FASDPN "Organic Brain Dysfunction and Prenatal Alcohol Exposure" Training, October 2000.

Susan Astley Hemingway Ph.D. worked with a software programmer to design and develop *FAS Facial Photographic Analysis Software* that allows clinicians and researchers to accurately and efficiently measure the magnitude of expression of the FAS facial phenotype from photographs for diagnosis and screening. This software was originally developed in 1996 with funding support from the Washington Research Foundation. In 2002 funds were received to develop a Windows-based, user-friendly version that is available for distribution to medical professionals. The software was updated in 2012 and 2016. This software was used to screen all children entering long term foster care in the King County Foster Care Passport Program. The results of this screening were published in the J. Pediatrics (Astley et. al., 2002). This software is distributed free of charge and used worldwide to screen and diagnose the facial features of FAS (Fig. 7).

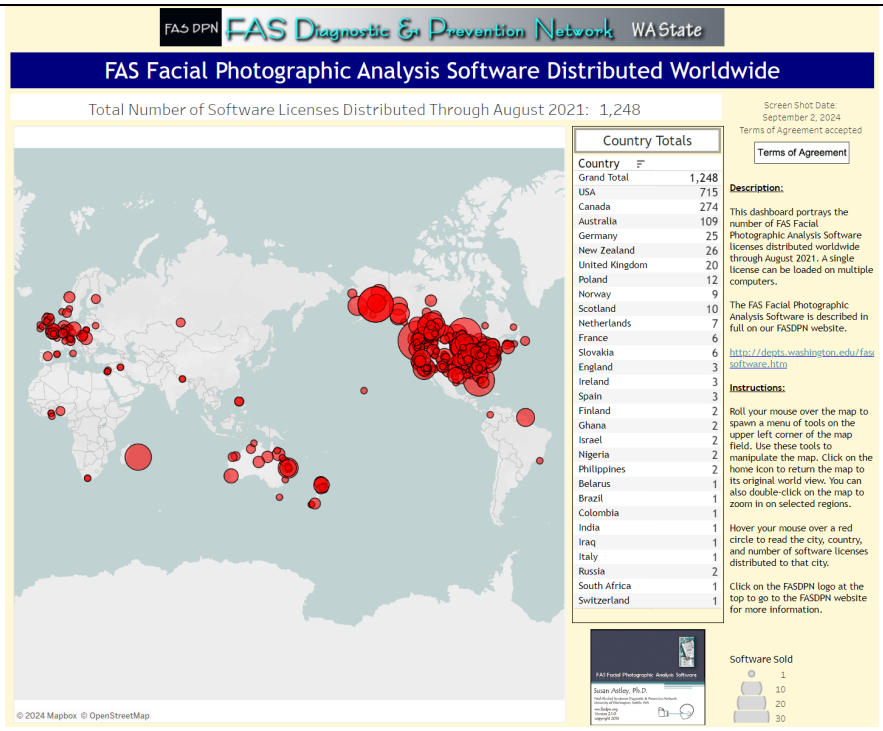


Figure 7. The FAS Facial Photographic Analysis Software has been distributed to thousands of clinicians and researchers in over 40 countries.

IV.B. FASDPN Training Programs

The U.W. FASDPN core site provides eight different FASD training programs targeted to families and professionals from WA State and around the world. Each is described below. Those marked by an asterisk are funded by this HCA contract.

1. **Training FASDPN Network Clinic Sites in Washington State***
   Over the years, there have been six FASDPN Satellite clinics in Snohomish, Pierce, South King, Yakima, Spokane and Whitman counties. In 2018, a 7th Network clinic "Hope Rising" (located in Bothell, King/Snohomish Counties) commenced training and opened in May 2019. Each Satellite clinic was locally owned and operated. Each received continuing education to stay abreast of the latest developments in diagnosis and prevention and to ensure diagnostic consistency across all sites. The continuing education is provided in two forms: 1) onsite consult on the diagnosis of patients evaluated at the Satellite clinics and 2) periodic one-day training sessions on key topics such as diagnosing organic brain damage. Each clinic sent the University of Washington the diagnostic files on all patients diagnosed. These files are reviewed for diagnostic accuracy. Feedback was provided to each clinic periodically throughout each year. A brief summary of selected one-day trainings is presented below.

   1998 FASDPN Clinic Coordinator Conference
   Six clinic coordinators attended a one-day training session. Topics included how to screen patient requests for clinic appointments, how to complete the FAS Diagnostic Evaluation Form, how to take properly aligned clinic photos, how to compose response letters to caregivers requesting appointments and how to bill for services.

   1999 Assessment of Brain Function
   The first annual one-day training session for Satellite clinics was held in Seattle. Sixteen professionals from the FASDPN Satellite clinics including psychologists, occupational therapists, speech language pathologists, and physicians attended. This session provided additional training on how to assess brain function in the FASDPN clinics. The 1999 edition of the FASDPN Psychometric Training Guide was distributed.

   2000 Organic Brain Dysfunction and Prenatal Alcohol Exposure
   The second annual one-day training session for Satellite clinics was held in Yakima, WA. Forty-six professionals from the FASDPN Satellite clinics including psychologists, occupational therapists, speech language pathologists and physicians attended. This session provided additional training on how to assess minimal brain dysfunction in the FASDPN clinics. he 2000 edition of the *Intervention Ideas Guide* was distributed.

   2002 Assessment of Brain Function
   The third annual one-day training session for Satellite clinics was held in Yakima WA in May, 2002. Fifty-two clinical team members from the FASDPN Satellite clinics attended. The FAS Facial Photographic Analysis Software was distributed to each clinic site.

   2004 Assessment of Brain Function
   The fourth annual one-day training session for Satellite clinics was held in Yakima WA in May 2004. Twenty nine clinical team members from the FASDPN Satellite clinics attended. The primary focus was review of the upcoming CDC FAS Diagnostic Guidelines and the 3rd edition of the Diagnostic Guide for FASD.

   2006 FASD Diagnosis and Intervention
   The fifth annual one-day training session for Satellite clinics was held in Yakima WA in May 2006. Fifty-seven clinical team members from the FASDPN Satellitel clinics attended. Preliminary outcomes of the following FASDPN research projects were presented:

MRI/MRS/fMRI study, Family Intervention study, Sensory Processing study, and the Social Communication Intervention Study.

2018 Diagnostic Team Training of the Wonderland Hope Rising FASDPN Network Clinic.
The Wonderland Developmental Center commenced training to become a FASDPN Network Clinic. Hope Rising opened their clinic in May, 2019.

2. **Training WA State Professionals at the U.W. FASDPN Clinic***
The University of Washington FASDPN core staff provides FASD training to community professionals throughout WA State A total of 5,739 professionals have been trained to date (Table 1). Trainees learn what FASD is and how it is diagnosed; who benefits from a FASD diagnostic evaluation; what services the FASDPN clinics provide and how to utilize them; and what their role is in the referral, diagnostic, and service provision process. These trainees have included the state social workers receiving professional development training through the UW Alliance for Child Welfare Excellence. The U.W. FASDPN clinic is open each week to visiting professionals who want to gain an understanding of our unique, comprehensive evaluative model. Trainees attend a 30-minute introductory lecture and observe the clinical team conduct FASD diagnostic evaluations on two patients. The clinic staff members are available throughout the day to guide the trainees and answer their questions. Included in our list of visitors was Washington State's First Lady Mrs. Mary Lowry, Ohio State's First Lady Mrs. Hope Taft, Dr. Faye Calhoun from the National Institute of Alcohol Abuse and Alcoholism, Dr. Sami Noursi, Director National FAS Center for Excellence and Jose Cordero, M.D., Director, CDC. The clinic hosts 150-250 professionals annually. The community professionals have expressed very high satisfaction with the training. Over 90% gave the training the highest possible score of 'excellent'.

In 2020 and 2021, trainings (and diagnostic evaluations) at the University of Washington clinic were interrupted by the COVID pandemic. The COVID pandemic closed the UW clinic from March through June 2020. The clinic re-opened July 2020. COVID safety policies at the UW Medical Center limited the number of trainees we were permitted to host in person in clinic. In addition, HIPAA policies prevented us from hosting trainees via Zoom. By July 2021 the UW Medical Center permitted trainees to attend both in person and via Zoom. In fiscal year July 2023-June 2024, the UW FASDPN held 35 clinics (2 patients per clinic) and trained 406 community professionals (in person and via Zoom). COVID safety policies continued to be followed.

Table 1. Total number of professionals trained by the University of Washington FASDPN Clinic.

Profession	N
Medical	1,454
Professional student	1,261
Psychologist, therapist, counselor, social worker	1,250
Administrator, coordinator, director	501
Educator, teacher	450
Alcohol treatment or chemical dependency counselor	152
Legal system	289
Other or not specified	436
TOTAL	5,793

3. **Off-site Training of Community-based Clinics or Institutions in WA State***
One-day didactic lectures on referral, diagnosis, and treatment planning of individuals with prenatal alcohol exposure are provided upon request to groups within WA State that provide services to high-risk populations and have requested training/diagnostic services in their

community. The number of trainings conducted to date are too numerous to list. Selected trainings are listed below. Webcasts of selected presentations are posted on the FASDPN website to increase access to training.

- Trained 30 JRA staff at Echo Glenn to address identification of and intervention with juveniles affected by prenatal alcohol exposure (1998).
- Provided diagnostic and primary prevention training and conducted special on-site diagnostic clinics for three WA State Native American tribes. (1997-1998).
- Trained JRA staff at Maple Lane School and DCFS foster care staff in King County on how to screen for FAS using facial photographs. (1998-ongoing).
- Conducted two lectures to DCFS, FCPP and DASA staff regarding outcomes of the FAS Screening in King County Foster Care (2002).
- Trained 200 members of the Skagit County FASD Juvenile Court Initiative including probation officers from the Skagit County Juvenile Court, officers from the courts of four tribal nations, staff from Youth and Family Services, ARIS and CHET (2005-06).
- FASDPN clinical members conduct 20-30 lectures annually to groups statewide requesting training/education on all aspects of FASD (family advocacy, adoption support, education, diagnosis, intervention, and prevention).
- The FASDPN clinical staff provided a half-day training of over 50 birth to three providers from the Experimental Education Unit at the University of Washington. Birth to three teachers from the Seattle Public Schools also attended. (2008).
- FASD: Focus on Executive Functioning Deficits. Hosted by NOFAS Washington State featuring speakers from the FASDPN. Aug 2010, Everett WA Target audience, families and professionals caring for individuals with FASD.
- FASD: From Discovery to Prevention in WA State. University of Washington Board of Regents. November 2011, Seattle WA.
- FASD: Focus on Intervention. Hosted by NOFAS Washington State featuring speakers from the FASDPN. March 2011, Everett WA Target audience, families and professionals caring for individuals with FASD.
- Institute on Human Development and Disability Core Seminar. FASD. Annually since October 2011, University of Washington. Target Audience: LEND Trainees, Birth to Three Trainees.
- Co-Occurring Disorders Conference. FASD: From Discovery to Prevention in WA State. Hosted by DSHS, DBHR, October 2011, Yakima, WA.
- FASD: Focus on Intervention. Hosted by NOFAS Washington State featuring speakers from the FASDPN, November 11, 2012, Everett WA. Target audience, families and professionals caring for individuals with FASD.
- FASD: Focus on Intervention. Hosted by NOFAS Washington State featuring speakers from the FASDPN, 2013, Everett WA. Target audience, families and professionals caring for individuals with FASD.
- Screening and referral of children with FASD. CHET Conference, April 2013, Seattle WA.
- Screening and referral of children with FASD. FCAP Conference, Sept 2013, Children's Home Society, Seattle WA.
- Developmental Medicine Teaching Rounds; FASD update presented by Dr. Astley Hemingway. October 2013, Seattle Children's Hospital.
- Advanced Practice in Primary Acute Care. FASD diagnosis, intervention and prevention. October 2013, Seattle WA.

- Astley Hemingway testimony on House Bill 2737 concerning fetal alcohol exposure. Invitation by Rep. Ruth Kagi, Chair Early Learning & Human Services Committee, Feb. 13, 2015. Olympia WA
- Webinar: Prevention of FASD, 2014, presented by Susan Astley Hemingway, sponsored by Association of Reproductive Health Professionals.
- Web-based "Talking with Patients about Alcohol Use During Pregnancy Clinical Minutes" 2016 sponsored by Association of Reproductive Health Professionals. Content contributed by Susan Astley Hemingway.
- Autism Clinic Rounds: FASD update presented by Dr. Astley Hemingway, October 2016, Seattle Children's Hospital.
- Demonstration of the FAS Facial Photographic Analysis Software developed by Dr. Astley Hemingway. 2016
- Developmental Medicine Teaching Rounds; FASD update presented by Dr. Astley Hemingway. March 2017, Seattle Children's Hospital.
- FASD from Discovery to Prevention; presented by Dr. Astley Hemingway to the Polish Institute of FASD. 2020
- Tacoma School psychologists: FASD training conducted by FASDPN psychologist Erin Olson PhD March 2022.
- WA-AK Neuropsychological Society: FASD training of 55 licensed psychologists in WA and AK by Dr. Astley Hemingway and Dr. Allison Brooks, April 2022.
- WA CHET: FASD training of 72 CHET personnel statewide by Dr. Hemingway, February 2023.
- Comparison of four international FASD diagnostic guidelines presented by Dr. Hemingway (keynote speaker) at the EUFASD international conference in September, 2024.
- Comparison of FASD diagnostic outcomes and PRAMS/BRFSS prenatal alcohol exposure histories over 20 and 30 years in AK and WA presented by Dr. Hemingway in February 2023 to the University of Alaska Anchorage CHD Project ECHO series (n = 55).
- Comparison of four international FASD diagnostic guidelines presented by Dr. Hemingway on April 13, 2024 at the International FASD conference held in Seattle WA (n = 98).
- Advancing justice for individuals with FASD across judicial systems by Dr. Julian Davies MD on April 11, 2024 at the International FASD conference held in Seattle WA (n = 250).

4. **Training of Washington State Students***
   University students from across WA State in medicine, nursing, speech and language, occupational therapy, education, dentistry and social work regularly attend clinic to observe how the interdisciplinary clinic manages this special population. A total of 1,261 students have attended clinic to date. Residents, fellows and interns from Pediatrics, Rehabilitation Medicine, and Psychology also rotate through the U.W. FASDPN clinic. Several students from Epidemiology, Speech and Hearing Sciences, Orthodontics, and Occupational Therapy and social work have earned their Master's and Doctorate degrees using the FASDPN database and patient population. One student won the nation's top student award for student research.

5. **Training for FAS Facial Screening and Diagnosis***
   The FASDPN provides training to medical and research personnel around the world on how to analyze facial photographs for screening and diagnosing the facial features of FAS. The FASDPN has worked with several hundred professionals to assess several thousand photographs. These professionals include staff from WA State Foster Care Passport Program, JRA, and the Skagit Juvenile Justice FASD Initiative. The FASDPN was contracted to provide FASD screening training for a multistate FAS Screening Program sponsored by SAMHSA from 2009-2012. In November 2011, the FASDPN participated in the NIH/CDC national meeting to formulate the

American Academy of Pediatrics endorsement of ARND. This work led to the inclusion of Neurodevelopmental Disorder-Prenatal Alcohol Exposed (ND-PAE) in the DSM-V in 2013.

6. **Training FASDPN Sites Outside Washington State**
The FASDPN conducts two-day training sessions on FAS screening, diagnosis, and prevention for clinical teams worldwide that would like to establish a FASDPN program in their community. These training sessions are held throughout the year. To date, over 255 teams worldwide have been trained. Our most intensive efforts in 2017-22 was focused on free training (enrollment in the FASD 4-Digit Code Online Course) for 50 clinicians in Slovakia and 47 clinicians in Poland. Trainees complete the FASD 4-Digit Code Online Course prior to their 2-day training in Seattle. In 2019, we trained a team from Poland and Dr. Astley Hemingway provided a keynote speech on International FASD Day (September 10, 2019) in Poland. The team in Poland established the Polish Institute of FASD in June 2020 and will serve as a center of excellence for FASD diagnosis using the FASD 4-Digit Diagnostic Code. Trainees in 2024 included clinicians from Israel, New Zealand, Mexico and the Netherlands. Over 1700 professionals from 40 countries have completed the FASD 4-Digit Code Online Course as displayed in the FASDPN Tableau Dashboard. The trainees spend the first day attending didactic lectures and receiving hands-on instruction in the specific screening and diagnostic techniques used by the FASDPN. The trainees spend the second day observing two interdisciplinary FASD diagnostic evaluations using the 4-Digit Code.

7. **Training via Video-teleconference, webinars and conferences**
The FASDPN provides FASD training to large, geographically dispersed audiences via video-teleconference, upon request. To date eight conferences/webinars have been held in 1999, 2000, 2004, 2009, 2010, 2011, 2012, 2013, 2014, 2017, 2018, 2022, and 2024 (Continuing Education for WA State nurses hosted by Children's Hospital and Regional Medical Center, FASD training via Alaska's ECHO program, training of medical and social service providers in Alberta and Ontario Canada, training FAS screeners nationwide hosted by SAMHSA, training of FASD interventionists nationwide hosted by the CDC, prevention webinar for healthcare professionals nationwide hosted by the Association of Reproductive Health Professionals). In 2017, three members of the FASDPN diagnostic team gave 5 FASD presentations at the 7th International Conference on "FASD Research: Results and Relevance; Integrating Research, Policy and Promising Practice Around the World" held in Vancouver BC. Hundreds of WA State professionals attended this conference. Three team members presented at the 2018 Adults with FASD International Conference in Vancouver BC and 7 team members presented at the 8th International Conference on FASD in Vancouver BC in 2019. Dr. Hemingway served as the keynote speaker at the 6th European Conference on FASD held in Norway in September 2022. Drs. Hemingway and Davies served as speakers at the 9th International Research Conference on Adolescents and Adults with FASD in April 2024 in Seattle WA.

8. **Answering Questions from Families***
The FASDPN staff answer several thousand questions annually from families and their care providers who call, send letters or leave questions on the FASDPN website (www.fasdpn.org).

IV.C. Screening and Surveillance

- A highly sensitive and specific, computerized FAS facial photographic screening/diagnostic tool was developed by the FASDPN in 1996 (Astley & Clarren, 1996). It was used to screen and

diagnose several thousand individuals. In 2003/2016, this photographic tool was upgraded to the FAS Facial Photographic Analysis Software by Dr. Astley Hemingway. Thousands of copies of the software have been distributed worldwide to date.

- A centralized, computer photographic analysis laboratory at the University of Washington FASDPN was established in 1998 and provides analysis of facial photographic data sets worldwide. Several thousand photographs have been analyzed to date. This service is supported on a self-sustaining revenue budget at the University of Washington.

- The FASDPN implemented computerized FAS photographic screening in two high-risk populations (foster care and juvenile justice) in 1999 in Washington State using the FAS Facial Photographic Analysis software developed by Dr. Astley Hemingway. All children/adolescents who screened positive (had the facial features of FAS) received a FAS diagnostic evaluation at a FASDPN Clinic. All children entering long term foster care in the King County Foster Care Passport Program were screened for FAS for 10 years with 98% participation. The prevalence of FAS in this foster care population was one out of every 100 children, or 10 to 15 times greater than the prevalence of FAS in the general population (1/1,000). The results of this screening were published in the Journal of Pediatrics (Astley, et al., 2002). Eight hundred and fifty adolescents in JRA were screened between 1999 and 2001. Several screened positive for FAS.

- The Washington State Birth Defects Surveillance System was an active surveillance system from 1986 to 1991. Since then, the system has been passive, relying on hospitals to report cases of children with birth defects. Currently, an enhancement project is in progress to develop a web-based, electronic reporting system to reduce the reporting burden to hospitals. The FASDPN reports all cases of FAS and Partial FAS to the State Birth Defects Surveillance Program annually.

- The FASDPN participated in the Skagit County FASD Juvenile Justice Initiative to establish methods to screen, diagnose, and intervene with youth entering the juvenile justice system. The project was one of five funded nationally by the SAMHSA FASD Center of Excellence. This national effort by SAMHSA to screen, diagnose, and prevent FASD was extended to 2012. SAMHSA utilized the screening and diagnostic tools and models established by the WA State FASDPN.

- The FASDPN participated in the National Children's Study to estimate the prevalence of FAS nationwide and in WA State. The photographic methodology established by the FASDPN to screen FAS in the King County Foster Care Passport Program was used.

- The FASDPN participated in the WA State Department of Corrections Adaptive Supports Program, Screening Offenders for Intellectual Disabilities, and Traumatic Brain Injury study. The FASDPN used the FAS Facial Photographic Analysis Software to screen facial photographs of study subjects for FAS (2013-2015).

- The FASDPN participated in the CDC-sponsored Danish Lifestyle During Pregnancy Study (2013-2019). The FASDPN analyzed 1,700 facial photographs for FAS using the FAS Facial Photographic Analysis Software. The study was published in 2019 (Kesmodel, Astley Hemingway et. al, 2019). The study documented low to moderate average alcohol consumption and isolated episodes of binge drinking in early pregnancy were associated with facial features

related to FAS in five-year-old children". The FASDPN hosted this Danish team to visit the UW FASDPN in May 2022.

IV.D. Prevention: Evidence of Success in WA State

Although FAS is entirely preventable, the factors associated with maternal alcohol use during pregnancy are complex and resistant to change. Maximizing primary prevention efforts will require targeting limited prevention resources to women at highest risk for producing children damaged by prenatal alcohol exposure. One of the highest-risk, identifiable populations are women who have already given birth to a child with FAS or given birth to a child with prenatal alcohol exposure and CNS dysfunction. A five-year Cooperative Agreement between the University of Washington and the CDC (Astley & Clarren, Co-Principal Investigators) demonstrated that these women can be identified and located through the diagnosis of their children in the Washington State FASDPN. Eighty mothers who currently live in Washington State and have given birth to a child with FAS were identified and extensively interviewed by members of the U.W. FAS Clinic team. The purpose of the interview was to generate a comprehensive profile of these women and identify factors that enhanced and hindered their ability to achieve sobriety or practice effective family planning. This baseline data was collected to develop an effective primary prevention program within the FASDPN. The results of this study were summarized in a 300-page final report to the CDC entitled "*Primary Prevention of Fetal Alcohol Syndrome: Targeting Women at High Risk through the FAS Diagnostic and Prevention Network 1992-97*". This report was submitted to DASA in 1998 and is posted on the FASDPN website. The results of this study were published in the peer-reviewed medical journal *Alcohol & Alcoholism* in 2000 (Astley et al., 2000a, 2000b). One of the key findings in this study was that after the diagnosis of the 80 children with FAS, 35 of their mothers gave birth to an additional 62 children, 75% of which were prenatally exposed to alcohol and 80% of which were born without the use of contraception. Although these 62 children were not formally followed to assess their cognitive/behavioral outcomes, it is known that a minimum of six have FAS. The goal of the FASDPN Primary Prevention Program will be to measurably reduce the risk of exposure and brain damage in these children.

Two programs to date have demonstrated that reduction in risk can be achieved. The Parent-Child Assistance Program (P-CAP), directed by UW Professor Therese Grant Ph.D., has demonstrated that a measurable reduction in risk factors leading to alcohol use and poor family planning (Grant et. al., 1996) can be achieved among pregnant women abusing drugs and alcohol. A key motivating force in P-CAP is the bond between the mother and her newborn. The women who will be targeted in the FASDPN program will not be pregnant for it will be paramount to target them before they conceive. This will present a unique challenge. The ongoing work by Dee Robertson, M.D. in Portland Oregon, however, provides compelling evidence that the risk of FAS can be reduced in women who are not currently pregnant (Interagency, 1997). Dr. Roberts has demonstrated that family planning and advocacy intervention targeted to high-risk Native American women reduced the incidence of FAS in their tribes to zero over a two-year period. The FASDPN will work collaboratively with P-CAP and will solicit consultation from Dee Robertson, M.D. in Oregon during the design and implementation of the FASDPN Primary Prevention Program. The estimated cost to society to raise a single child with FAS from birth to 18 years of age is one million dollars (Abel & Sokol, 1987). Prevention of just a single FAS birth can pay for up to ten years of the primary prevention program proposed below. This program has the potential for preventing many FAS births per year in Washington State.

One of the primary goals of the FASDPN is to identify the birth mothers of children diagnosed with prenatal alcohol exposure and cognitive/behavioral dysfunction and to link these high-risk women to community-based primary prevention services such as P-CAP to reduce their risk of bearing additional

children exposed to prenatal alcohol. The FASDPN identified 80 birth mothers of children diagnosed with FAS in WA State in 1992-97 and has the potential of identifying an additional 70 birth mothers annually; birth mothers of children diagnosed with FASD through the FASDPN. During the 1998-99 fiscal year, the FASDPN maternal advocate (Diane Bailey, MSN) provided comprehensive advocacy services to three of these high-risk women, enrolled two additional women in P-CAP, and provided referral and support services to ten birth mothers who attended their child's diagnostic evaluation at the U.W. FASDPN clinic. Ms Bailey also provided in-service training on motivational interviewing and birth control to P-CAP advocates and participated in case conferencing, two to three times a month, at the Seattle and Tacoma P-CAP offices. In 1999, Ms Gendler, M.S.W. joined the FASDPN as the maternal advocate, replacing Ms Bailey who went on to work for the WA State Department of Health. A grant to establish and assess the FASDPN Primary Prevention Bridges Program was submitted to NIAAA in March 1999 in response to their FAS Primary Prevention request-for-proposals. This grant was submitted by Dr. Carmichael Olson (FASDPN clinical psychologist) and represents a collaborative effort between the FASDPN, P-CAP and the FAS Interagency Work Group. The grant proposed to establish and assess a primary prevention program (the First Bridges Program) that links high-risk women identified by the FASDPN to appropriate community-based primary prevention services. The proposal received a favorable review, but the reviewers requested pilot data be collected prior to re-submission. In response, the FASDPN piloted the "FASDPN First Bridges Program." This is an approach to primary prevention that is a natural extension of the existing FASDPN clinical services and uses empirically-supported brief intervention techniques.

The FASDPN First Bridges Program established a clinically feasible protocol for identifying, locating, and providing FAS prevention services to eligible high-risk women who have given birth to an alcohol-exposed child with confirmed evidence of CNS dysfunction. These women were still fertile and either actively drinking or at high risk for relapse. Aims of the prevention services were to: (1) Enhance the woman's "readiness to change" her alcohol and/or contraceptive use; and (2) Reduce self-reported "need for help" via brief intervention and linkage with community services. The results of this study were published in Alcoholism: Clinical and Experimental Research, 2002 (Carmichael et al., 2002).

In the course of providing services to the pilot group of birth mothers, FASDPN staff received training on the issues and concerns of women giving birth to children with alcohol-related disabilities. A social work internship training program was initiated, with the first student completing a nine-month practicum focused on the First Bridges Program. Data on the needs and issues of birth mothers, and methods of FAS prevention, were part of the quarterly FASDPN trainings.

WA State is Successfully Preventing FAS: The prevalence of FAS is estimated to be 1 to 3 per 1,000 live births and is the leading known cause of intellectual disabilities in the Western World. To prevent FAS, maternal alcohol consumption during pregnancy must be reduced. To assess the effectiveness of FAS prevention efforts, one must be able to accurately estimate the prevalence of FAS over time in population-based samples. Accurate estimates of prevalence, in turn, require accurate diagnostic methods. With the establishment of the Washington State FAS Diagnostic and Prevention Network (FASDPN) of clinics, the development of the FAS Facial Photographic Screening/Diagnostic Tool, the creation of the FAS 4-Digit Diagnostic Code, the establishment of the Foster Care FAS Screening Program, and the collection of Pregnancy Risk Assessment Management System (PRAMS) data on maternal use of alcohol during pregnancy, the tools, methods and infrastructure for assessing the effectiveness of FAS primary prevention efforts in Washington State are in place. An overview of the history of FASD from discovery to prevention in WA State is presented in a webcast by Susan Astley

Hemingway PhD (Seattle Children's Grand Rounds August 2012). A cross-sectional study was conducted to determine if the prevalence of FAS among children in a foster care population, born between 1993 and 1998, decreased with the documented decrease in prevalence of maternal use of alcohol during pregnancy from 1993 and 1998 in Washington State. The prevalence of maternal drinking during pregnancy in Washington State declined significantly ($p < 0.001$) from 1993 to 1998 as did the prevalence of FAS among foster children born from 1993 to 1998 ($p < 0.03$). These observations strongly support that FAS prevention efforts in Washington State are working (Astley, 2004). The results of this study were published and showcased on King5 News in Seattle as an important public health message.

A comprehensive summary of WA State efforts to prevent FASD from 1968-2004 is posted on the WA FASD website in a document entitled FASD: WA State History. It is paramount that WA State sustain its successful efforts to reduce FASD. Unfortunately, the most recent PRAMS data documents a steady increase in maternal reporting of drinking during pregnancy, in contrast to the steady decline observed in the 1990s. Preliminary data documents this increase in drinking is associated with an increase in prevalence of FAS in foster care among children born after 1998. Most recently, data from the FASDPN confirms that the incidence of FAS is dropping significantly in WA across birth cohorts spanning 1940 through 2009 (see Tableau Dashboard).

IV.E. Intervention

The FASDPN has engaged in all levels of FASD intervention from guiding public health policy to conducting randomized control trials to establish an evidence base for intervention efforts. These efforts to date are summarized below.

- Diagnosis leads to successful interventions. Twenty years of patient surveys confirm FASD diagnostic evaluations conducted by the WA FASDPN afforded patients substantial access to interventions that met their needs (Astley, 2014).
- NOFAS WA (now FASD Focus NW). Directed by Julie Gelo, B.A. Established in 2006, the mission of FASD focus NW is to educate, advocate and support individuals with FASD and their families. They envision building bridges that connect and unify professionals, individuals with FASDs, families, and community members.
- Family Intervention: Families Moving Forward" (FMF) is a CDC-sponsored, intervention research project, conducted through the FASDPN, exploring evidence-based services for children with fetal alcohol spectrum disorders (FASDs), their families, and the professionals who care for them. The program was established by a Professor of Psychology from the FASDPN, Dr. Heather Carmichael Olson PhD. At its heart, the FMF intervention model is aimed at: 1) providing ongoing support to parents and helping them better understand their challenging children 2) helping parents hone skills they already have, while adding specialized parenting techniques to their care-giving repertoire, 3) adding value to community resources and providers that families find helpful, 4) helping families boost their progress in a positive direction, giving them reason to be more optimistic about the future, and helping reduce the chance their children will have secondary disabilities later in life. This project completed it's tenth year of funding in 2010. Sixty WA State families raising children with FASD received 9 months of in-home intervention services for free. FMF is now a program available to WA families. In 2017, Dr. Jirikowic, the OT on the FASDPN diagnostic team submitted a grant to expand the FMF program to focus on infants, birth to three.
- SNACS Clinic: The SNACS Clinic model (developed through the FMF program) is a short-term assessment and consultation service (3 to 5 sessions) using materials from the FMF Program. The

research and clinical team is led by Dr. Heather Carmichael Olson and Dr. Michelle Kuhn. SNACS services are carried out by providers with advanced degrees in clinical or school psychology. This "Specialized Neurodevelopmental Assessment and Consultation Service" (SNACS) offers: (1) mental health diagnosis of conditions on the fetal alcohol spectrum (and co-occurring mental health issues); (2) customized referrals and ideas for linkages to community resources; and (3) tailored short-term consultation on issues important to individual children and families.

- Brooks Powers Group Assessment Team: Established by a psychologist serving in the FASDPN (Allison Brooks PhD), provides a range of assessments at the request of caregivers and schools. Their evaluations are intended to provide information about a child's profile of strengths in addition to identifying potential diagnoses and areas in need of intervention and support. Their providers have experience and training in FASD and understanding how information obtained from a clinical evaluation is used in an educational setting. They aim to provide information that can be useful in the process of developing educational plans, counseling and therapy interventions, parenting supports, and helping care providers coordinate services.
- Sound Families Pediatric Therapy: Established in 2024 by an occupational therapist from the FASDPN (Jennifer Nash PhD, OTR/L, IMH-E). With expertise in FASD, Dr. Nash provides OT services via telehealth for families of children 0-9 years old. Dr. Nash has been serving families in the Puget Sound community and beyond for more than twenty years as a pediatric occupational therapist and infant mental health specialist with multiple areas of focus including early intervention, trauma-informed care, child development, challenging behaviors, and sensory processing.
- DDA Eligibility Criteria: In 2015, the FASDPN worked effectively with the WA Developmental Disabilities Administration (DDA) leading to the acceptance of FASD for determination of eligibility for DDA (DDA Management Bulletin D15-012, March 13, 2015). "Diagnoses of a condition that is similar to Intellectual Disability and attributable to prenatal maternal consumption of alcohol may be accepted as an "another neurological or other condition similar to Intellectual Disability" under 388-823-0600. The diagnosis must be supported by evidence confirming prenatal alcohol exposure. This evidence may be found in medical records or other documentation."
- Early Support for Infants and Toddlers (ESIT) qualifying diagnoses: In 2020, the FASDPN worked effectively with ESIT leading to the acceptance of prenatal alcohol exposure as a qualifying condition for ESIT.

IV.F. Systematic Information Retrieval and Tableau Dashboards

In 1995, Dr. Astley Hemingway began the development one of the world's largest, most comprehensive clinical databases on FASD with patient consent and University of Washington Human Subjects approval. The data allows the FASDPN to track regional FASD diagnostic demand, diagnostic capacity and diagnostic outcomes over time. It also allows the FASDPN to develop state-of-the-art screening and diagnostic tools and support intervention research that directly benefits WA children and their families living with FASD. The database contains information on over 5,000 families requesting diagnostic evaluations and over 3,000 patients who have received diagnostic evaluations. There are over 3,000 fields of information on each patient. A seminal report profiling the first 1,400 patients evaluated at the WA FASDPN was published in 2010 (Astley, 2010). Over 100 peer-reviewed publications have been published in the medical literature by FASDPN clinical team members using the data from the FASDPN database. The database has also supported a multitude of Master's Theses and Doctoral Dissertations by graduate students in public health, psychology,

medicine, nursing, dental, social work, speech-language and occupational therapy. The database also serves as a patient registry allowing patients to enroll in FASD research studies that often provide direct benefits to participants (e.g., free neuropsychological and medical assessments, free intervention services, etc.). This patient registry paved the way for the development of the evidence-based Families Moving Forward FASD intervention program established and directed by Heather Carmicheal Olson.

An Institutional Review Board application was submitted to the University of Washington Human Subjects Division on September 5 1995 for approval to collect, store and summarize data collected in by the UW FASD clinic. The application was approved on September 28 1995 and now has ongoing approval. All procedures are HIPAA compliant. All staff received HIPAA and IRB training. A copy of the initial approved application was submitted in Appendix H of the Year 01, Quarter 01 Report in 1995. As per IRB policy, all research studies proposing to enroll study subjects from the FASDPN are required to submit separate IRB applications. In May 2000, the UW FASDPN clinic database received University of Washington IRB approval to serve as a FAS Research Registry. This UW IRB zipline application has been renewed as an ongoing study with no end date. This facilitates the invitation and voluntary enrollment of patients with prenatal alcohol exposure into clinical research studies designed to identify effective interventions and diagnostic tools. Several million dollars in funding was received in 2001-2010 from the CDC and NIAAA to conduct these clinical research studies, providing several hundred WA State families and children with free medical care and intervention services.

With the advent of "Interactive Data Platforms", Dr. Astley Hemingway has constructed and launched an endless array of Tableau dashboards that allow people worldwide free, interactive access to the entire FASDPN database (in aggregate format without identifiers). Included are dashboards entitled FASD Diagnoses by WA State County; 4-Digit Code FASD Diagnoses Worldwide; FASD WA State FASD Diagnostic Outcomes by Patient's Birth Cohort, etc.).

In 2024, Dr. Astley Hemingway along with colleagues in Alaska published a seminal paper entitled "*WA and AK Statewide FASD Diagnostic Clinical Networks: Comparison of Three Decades of 4-Digit Code Diagnostic Outcomes and Prenatal Alcohol Exposure Histories*". FASD screening, diagnosis, intervention, research and prevention hinges on establishment of interdisciplinary FASD diagnostic clinics using an evidence-based method of diagnosis. In 1993, Washington State opened the first interdisciplinary FASD diagnostic clinic sponsored by the CDC as a FASD primary prevention study. Clinic data was used to develop the evidence-based FASD 4-Digit Diagnostic Code, paving the way for the clinic's expansion into a Statewide network of FASD diagnostic clinics (Washington Fetal Alcohol Syndrome Diagnostic & Prevention Network), now in its 31st year. Alaska adopted this Washington model in 1999. Both States have also participated in the CDC Pregnancy Risk Assessment Monitoring System and Behavioral Risk Factor Surveillance System since the 1990s. Study objectives were to describe the two Statewide FASD diagnostic networks; graphically compare the 4-Digit-Code FASD diagnoses and Prenatal Alcohol Exposure (PAE) over 2-3 decades and illustrate how network data helped guide FASD public health policies and track successful prevention efforts. Both States demonstrated the feasibility and value of establishing Statewide interdisciplinary FASD diagnostic clinical networks using the FASD 4-Digit-Code. Legislative support, centralized data collection, and use of a single, evidence-based FASD diagnostic system have been key to the long-term, ongoing success of these two diagnostic networks.

V. Funds Attracted to WA State (over 15 million dollars for WA children and families)

The University of Washington Core FASDPN clinic has successfully obtained over **15 million dollars** in additional funding to support FASD screening, diagnosis, and intervention for families in

Washington State. Hundreds of WA State families and children have received free medical care and intervention services through these public health/research activities. Washington State's support of the FASDPN was instrumental in our being able to attract these funds and service opportunities to our State. The Washington State FASDPN continues to work directly with the NIAAA, CDC, NIH, FASD United and SAMSHA in a national effort to diagnose and prevent FASD.

1. *Centers for Disease Control*. FAS Prevention through development of first FASD interdisciplinary diagnostic clinic at the University of Washington This funding established the Core WA FASDPN clinic. (1992-1997).

2. Funding Source: *Washington Research Foundation* Title: Development of the FAS Facial Photographic Screening/Diagnostic Software. The FASDPN developed software to allow medical professionals to analyze facial photographs for the presence of FAS facial features. This software was used to screen all children entering the King County Foster Care Passport Program for FAS from 1999 to 2009. This software is also used in all FASDPN diagnostic clinics. Funding period: 8/1/02 through 2/28/03. Total Costs: $ 10,000.

3. Funding source: *Centers for Disease Control.* Title: Intervening with children with FASD. This study provided 60 WA State families raising children with FASD free in-home intervention for 9 months. Study period: 9/30/01 through 9/29/10. Total Costs: $2,396,497.

4. Funding Source: *National Institutes of Alcohol Abuse and Alcoholism*. Title: MRI/S in children/adolescents with FASD. This project used (magnetic resonance spectroscopy (MRS), magnetic resonance imaging (MRI), and functional MRI (fMRI)) to determine if prenatally alcohol-exposed children, with and without FAS, who present along the full continuum of mild to severe cognitive/behavioral dysfunction, have irrefutable evidence of organic brain damage in the form of chemical, structural and/or functional alterations of the brain. Sixty WA State children with FASD received free neuropsychological assessments and MRI scans. Study period: 03/01/02 through 02/28/06. Total Costs: $ 996,694.

5. Funding Source: *National FAS Center of Excellence.* Title: FAS Summer Conference. The objective of the summer camp conference was to bring together families raising children with FASD for the purpose of having fun and networking with other families and community professionals. Funding Period: August 28-31, 2003. Total Costs: $35,000.

6. Funding Source: *University of Washington Educational Outreach and Technology Transfer*. This project supported the development of the FASD 4-Digit Diagnostic Code online course targeted to medical/social service providers. Over 600 professionals have completed the course to date. Funding Period: 2003. Total Costs: $56,000.

7. Funding Source: *SAMSHA FASD Center of Excellence*. FASD Screening, Diagnosis and Intervention in Juvenile Justice. 8/2004 through 7/2007. Subcontract to FASDPN. Total Costs: Over $200,000. FASD Screening, Diagnosis and Intervention in High-Risk Populations. 6/2008 through 5/20012. Subcontract to FASDPN. Total Costs: $50,000.

8. Funding Source: *SAMSHA FASD Center of Excellence*. Provide consultation on national FASD screening, diagnosis and intervention in high-risk populations. 6/2008 through 5/20012. Subcontract to FASDPN. Total Costs: $12,000.

9. Funding Source: *National Institutes of Alcohol Abuse and Alcoholism*. Title: Sensorimotor Intervention to Affect Balance, Engagement, and Learning for Children with FASD. This study is providing WA State children with FASD free sensorimotor interventions. Funding period: 2009-2015. Total Costs: $1,000,000.

10. *Centers for Disease Control:* Arctic FASD Regional Training Center. The FASDPN team is serving as consultants for Alaska's creation of a CDC-sponsored FASD Regional Training Center. (2009-2017).

11. *National Institutes of Health:* National Child Study. The FASDPN took the lead in establishing the methodology for assessing facial anomalies from photographs for 100,000+ children who will be enrolled from birth to 21 years of age in the country's largest ever longitudinal study of child development. This study will allow the FASDPN to estimate the prevalence of FAS in the U.S. general population as well as the WA State population. (2010-2012).

12. *FASD United Policy & Training Center* https://nofaspolicycenter.org/.

13. UW ADAI; Title: Language Learning in Children with Neurodevelopmental Disorders. Kover PI. This study enrolled 50 patients from the FASDPN clinic. The children were provided free language assessments. (2016-18): Total Costs: $29,900.

14. UW ADAI; Title: Characterizing Auditory Processing in Individuals with FASD. McLaughlin PI. This study enrolled 15 children from the FASDPN clinic. These children received free language and auditory processing assessments (2016-18) Total Costs $29,586.

15. UW Rehabilitation Medicine; PhD Dissertation (2024) Title: Toward earlier identification and strength-based intervention for infants and toddlers with prenatal alcohol exposure: Evidence from the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network Clinical Database. Key finding: The majority of infants/toddlers presented with clinically significant delays in development, sensory processing and/or behavioral functioning. Adverse developmental outcomes were significantly correlated with PAE and/or postnatal risk factors. Early diagnosis led to early intervention.

16. "Advancing FASD Research, Prevention and Services Act" FASD Respect Act authorizes $50 million for FASD prevention efforts, screening and identification and FASD-informed services by federal, state, local, tribal and private stakeholders. The FASDPN team in conjunction with FASD United advocated for this congressional act in February 2021 in conference calls with Senator Patty Murray's office. This Act continues to receive endorsements from senators nationwide as of June 2024.

VI. References and Key FASDPN Research Publications:

FASD Research: The UW FASD diagnostic clinic started in 1993 as a CDC-sponsored FASD prevention research study (Astley, et al., 2000a, b). Over the next 3 decades, the core FASDPN clinic at the University of Washington has engaged in a multitude of research studies resulting in over 100 peer-reviewed publications. The FASDPN completed an NIAAA-sponsored research study assessing the diagnostic value of magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) and functional MRI (fMRI) in 2009. These non-invasive tools allow medical professionals to assess the impact alcohol had on an individual's brain structure, brain chemistry, and brain function. This research would not have been possible without the FASDPN and its large clinical/research patient population. The results confirm the validity of these diagnostic tools and confirm that children along the full spectrum of FASD (not just the subset with full FAS) present with clear evidence of brain damage. The results are published in the peer-reviewed medical literature (Astley et al., 2009a, 2009b, 2009c, 2009d). A comprehensive report documenting the validation of the FASD 4-Digit Diagnostic Code was published by Astley in 2014. In 2016, the FASDPN clinical team published a seminal paper documenting the essential role of growth deficiency in the diagnosis of FASD (Astley et al., 2016). Growth deficiency is a powerful predictor of which infants with prenatal alcohol exposure will present with severe brain dysfunction later in childhood. In 2019 the FASDPN clinical team published the world's largest twin study in FASD confirming that fetal genetics contributes to fetal vulnerability to prenatal alcohol exposure (Astley, et al., 2019). The FASDPN also published a comprehensive assessment of 4 FASD diagnostic systems worldwide documenting the superior performance of the FASD 4-Digit Code. (Astley et al., 2019) Dr. Hemingway was invited to present this study to the European Union FASD meeting held in Norway in 2022 and the International FASD Conference in 2024 held in Seattle. As of 2024, the annual International FASD Conference that has been held in Vancouver BC for over 15 years will now be hosted in Seattle. In 2020, the FASDPN published seminal studies documenting the high specificity of the 4-Digit Code FASD facial phenotype (Astley et al., 2020a) and confirming prenatal alcohol exposure as the dominant risk factor among children presenting with neurobehavioral impairments (Astley et al, 2020b).

All publications written by members of the FASDPN are posted on the FASDPN literature website as free, downloadable pdf files. Below are selected publications sorted alphabetically by first author.

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