Neurodevelopmental Follow-up of Preterm Infants

What Is New?

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KEYWORDS

- Neurodevelopment • Cerebral palsy • Premature infants
- Developmental coordination disorder • Language • Socioeconomic status

KEY POINTS

- Although the rate of severe cerebral palsy (CP) has decreased among preterm infants, the rate of mild CP and the identification of developmental coordination disorder (DCD) have increased in this population.
- DCD has been shown to have effects persisting throughout school age and adolescence.
- There is increasing recognition of the importance of early interactive language exposure on the language development of infants.
- Although maternal education level continues to be the most frequently reported socioeconomic status indicator, there is increasing evidence of the impact of psycho-socioeconomic adversities on preterm neurodevelopmental and behavioral outcomes.
- Identification of adverse maternal mental health in the neonatal ICU and postdischarge provides an opportunity for intervention in former preterm infants and their mothers.

There is increasing evidence of ongoing changes occurring in short-term and long-term motor and language outcomes in the preterm population. In addition, there is increased awareness of the negative impact of family psycho-socioeconomic adversities on preterm outcomes. This review provides updates on 3 areas of reported change in neurodevelopmental follow-up and outcomes in preterm infants: motor impairments, language delays and disorders, and the impact of family psycho-socioeconomic adversities on outcomes.

MOTOR IMPAIRMENTS AMONG PRETERM INFANTS—A CHANGING PICTURE

Modern neonatal intensive care has contributed to increased survival of infants at the limits of prematurity,[1–4] and changes in the rates of neonatal morbidities[5] and

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neurodevelopmental impairments.[1,3] A key component of neurodevelopmental impairment is cerebral palsy (CP).[6] During the early years of neonatology, a primary focus of follow-up studies was on identification of rates of CP.[7–9] CP is often associated with other long-term sequelae, including cognitive, sensory, and language impairments; seizure disorders; and growth abnormalities. Confirmation of this diagnosis is difficult to achieve before 18 months to 24 months of age, especially if the manifestation is mild. Categorization of degree of CP severity based on the Gross Motor Function Classification System[10] into mild (level 1), moderate (levels 2 and 3), and severe to profound (levels 4 and 5) is well accepted.

Recent studies suggest changes in both the rates of CP and the degree of severity.[5,11–14] The Neonatal Research Network study of extreme preterm infants less than or equal to 27 weeks' gestation born from 2011 to 2014 and evaluated at 18 months to 26 months of age showed that the rate of CP decreased during this time period from 16% to 12%.[5] In addition, whereas the rate of severe CP decreased by 43%, the rate of mild CP increased by 13% during the study period. An additional 19% of children had a suspect neurologic examination. This indicates that improvement of motor outcomes is occurring in conjunction with the increased survival of the most preterm neonates. This finding supports that just as there is a spectrum of white matter abnormalities among preterm infants, there is a spectrum or continuum of motor findings ranging from mild to profound.[15,16]

Former preterm infants are at risk of a range of motor abnormalities, including delayed motor milestones, balance abnormalities, challenges with manual dexterity, and generalized coordination abnormalities now codified as developmental coordination disorder (DCD) with the Movement Assessment Battery for Children (MABC)–Second Edition (MABC-2).[17–19] The American Psychiatric Association in 2013 defined DCD as impairment in coordinated motor skills that significantly interfere with performance in everyday activities. Abilities assessed include manual dexterity, aiming, and catching and balance. Scores above the 15th percentile are considered normal, scores in the 6th to 15th percentiles are at risk, and scores in less than or equal to the 5th percentile are consistent with significant motor difficulty. Although motor delays are evident in early childhood, the diagnosis of DCD is often not made until school age.[20] A series of studies reporting DCD at ages 3 years to 24 years is shown in **Table 1**.

Kwok and colleagues[21] examined the predictive value of the MABC-2 at 3 years to predict DCD at 4.5 years among very preterm (VPT) children, defined by the investigators as 24 weeks' to 32 weeks' gestation, and reported a sensitivity of 90% and specificity of 69%, indicating many false-positive results. The investigators concluded that at this early age, the MABC is highly sensitive but with limited specificity in identifying VPT children who are at risk of DCD. The Griffiths and colleagues' study[22] reported that 25% of infants born at less than 30 weeks' gestation had scores consistent with significant motor difficulty ($\leq$5%) at both 4 years of age and 8 years of age, and the MABC-2 at 4 years had high sensitivity (79%) and specificity (93%) for predicting motor impairment at 8 years. Bolk and collegues[23] examined a large cohort of apparently healthy extreme preterm infants (defined as 22–26 weeks' gestation) compared with term controls at 6.5 years of age and reported the highest rate of DCD of 37.1% in preterm infants versus 5.5% in term infants. Three studies from the Victorian Infant Collaborative Study Group[24] of infants born at 22 weeks' to 27 weeks' gestation identified consistently low but increasing rates of DCD during 3 time periods between 1991 and 2005, with increasing rates of 2%, 8%, and 7%. The findings are similar to those of Setanen and colleagues[25] in a Finish cohort at 11 years of age. Finally, a study[26] from Norway reported rates of DCD of 29% in a

Table 1
Developmental coordination disorder

Authors, Year Published	Gestational Age	Date of Birth or Visits	Sample Size	Age of Assessment	Movement Assessment Battery for Children Coordination Disorder
Kwok et al,[21] 2018 Canada	24–32 wk	Visits 2010–2015	165	3 y 4.5 y	Prediction Sensitivity 90% Specificity 69%
Griffiths et al,[22] 2017 Australia	<30 wk	2005–2007	96	4 y 8 y	<5th% 25th% 25th%
Bolk et al,[23] 2018 Sweden	22–26 wk	Birth 2004–2007	229 preterm 244 term	6.5 y	<5th% Preterm 37.1% Term 5.5%
Davis et al,[28] 2007 Australia; Victorian Infant Collaborative Study Group	22–27 wk	Birth 1991–1992	163	8 y	<15th% 10% <5th% 2%
Roberts,[27] 2011 Australia; Victorian Infant Collaborative Study Group	22–27 wk	1997	132 154 term	8 y	EP <15th% 23% EP <5th % 16% T <5th% 5%
Spittle et al,[24] 2018 Australia: Victorian Infant Collaborative Study Group	22–27 wk	1991–2005	Study Year 1991–1992 226 1997 172 2005 189	8 y	<5th% 2% <5th% 8% <5th% 7%
Setanen et al,[25] 2016 PIPARI Study Group Finland	23–35 wk	2001–2004	82	11 y	<5th% 8%
Husby et al,[26] 2013 Norway	VLBW <1500 g	1986–88	36 VLBW 37 term	14 y 23 y	<5th% 29% <5th% 29%

small cohort of former very-low-birthweight (VLBW) infants, less than 1500 g, born from 1986 to 1988 at both ages 14 years and 23 years. At 23 years, the VLBW subjects had poorer total motor scores and subscores for manual dexterity and balance compared with the term comparison group. After exclusion of the 4 VLBW subjects with CP, however, the difference in total MABC-2 score between study groups was no longer significant.[26] This study has a small sample size and the results need to be replicated in larger studies. The percentage identified in reports are impacted if children with CP are excluded.[27] The findings overall suggest that early motor coordination challenges among former preterm infants have lasting effects.

Risk factors of DCD include preterm birth, male gender,[28] and decreased brain volume at term age.[25] Setanen and colleagues[25] propose that volumetric brain MRI at term age may provide a tool to identify infants at risk for later neuromotor impairment. Relative to longer-term outcomes, CP is fairly consistently associated with a spectrum of more severe neurosensory morbidities, including seizure disorders, blindness, and hearing impairment.[29] In addition to coordination deficits, including difficulties writing and balancing, DCD can be associated with academic challenges, behavior problems, and decreased participation in sports.[30] At school age, DCD is associated with lower cognitive and academic test scores and greater behavior problems.[28]

Prenatal medical interventions, including antenatal steroids[31] and magnesium sulfate,[32,33] and neonatal interventions, including indomethacin[34] and caffeine,[35,36] have been shown associated with at least partial reduction in rates of CP and DCD. Several motor and education-based interventions have shown some efficacy in reducing the manifestations coordination disorder.[37–39] Steps can be taken in the neonatal ICU (NICU) to identify infants potentially at risk of CP or DCD, provide physical therapy/occupational therapy support during the NICU stay, facilitate referrals to neurology for follow-up as needed, provide anticipatory guidance for parents, and refer all high-risk infants to early intervention programs at the time of discharge.[40,41]

PRETERM LANGUAGE IMPAIRMENTS: CAN MORE BE DONE TO IMPROVE OUTCOMES?

Early development of language is critically important because it is the building block for basic communication, cognitive processes, literacy, and social interactions. Preterm infants are at increased risk of speech and language morbidities, including mild to moderate delays/deficiencies in vocabulary development,[42] phonological processing,[43] language comprehension,[44] verbal short-term memory,[45,46] and grammatical development.[43] In addition to brain injury, environmental factors, including both nonwhite race and Hispanic ethnicity, have been associated with early speech and language delays among VPT infants with less than 1000-g birthweight. Black and Hispanic toddlers had lower language scores than whites at 18 months to 22 months, even after adjustment for confounders.[47] A Neonatal Research Network study reported that children born at less than 28 weeks' gestation whose primary language was Spanish had lower Bayley Scales of Infant and Toddler Development (BSID) language scores but similar cognitive scores compared with children whose primary language was English.[48] The investigators suggested the findings may, in part, be secondary to use of English language–based testing tools that introduce bias. In addition, low socioeconomic status (SES) is well known to be associated with alterations in the language environment, decreased early language exposure, and subsequent language delay.[49,50]

Responses to the language environment begin in fetal life. The cochlea of the inner ear completes development between 24 weeks' and 26 weeks' gestation, and auditory reception starts during this time period. Blink-startle responses to vibroacoustic stimuli are first elicited in the fetus at 24 weeks' to 26 weeks' gestation, with consistent responses by 27 weeks' to 28 weeks' gestation.[51] At 27 weeks' to 29 weeks' gestation, the hearing threshold in utero is approximately 40 dB. The fetus differentiates the maternal voice from a stranger's voice at approximately 32 weeks' to 37 weeks' gestation by changes in heart rate, suggesting a preattention reaction.[52] Fetuses have the ability to differentiate a maternal voice from a paternal voice.[53] Term infants prefer human voice to other acoustic stimuli and prefer a maternal voice to other female voices and to a paternal voice.[54–57]

The extreme preterm infant, however, leaves the protective sound environment of the uterus as early as 22 weeks' to 23 weeks' gestation and enters the noisy and stressful NICU nonoptimal language environment for extended periods of up to 2 months to 6 months. The first 3 years of age represent a sensitive period of brain plasticity, with the sensory environment impacting brain growth, structures, connectivity, and function.[58] Exposure of the preterm brain to the NICU environment alters neuronal differentiation, which may alter subsequent development.[59,60] The term infant, however, goes home in 1 day to 3 days and is exposed to the touch, talk, sounds, and social interactions within a typical family unit.

Despite the nonoptimal environment, the early preterm infant begins to respond to auditory stimuli by 24 weeks' gestation, with consistent responses by 28 weeks and distinct preferences shown for maternal voice.[61] Preterm infants have also been shown to respond to recordings of maternal sounds and voice by lowering their heart rate, which has been interpreted as increased infant relaxation.[62]

Should language intervention be provided in the NICU? It has been shown that increased exposure to early language experience for term children in the form of conversations and talk with family members is associated with improved child vocabulary size and IQ.[49,50] The authors' team investigated preterm vocalizations and the language environment of the NICU with 16-hour audio recordings of adult speech, child vocalizations, conversation turns (CTs), silence, and noise. The 2-oz recording device can be placed into a small vest the infant wears or can be placed immediately adjacent to the infant. Language Environment Analysis (LENA) speech-identification algorithms have been determined to be reliable, with 82% accuracy for adults and 76% accuracy for infants and children.[63] Output of a typical recording, which is used to provide feedback to the parent, is shown in **Fig. 1**. It is divided into 4 domains, including the audio environment, child vocalizations, CTs, and number of adult words spoken each hour. The printout is reviewed with the parents, awake times with high and low interactions are identified, and goals can be set for timing and intensity of child-directed conversations.

Study findings revealed that extremely-low-birthweight (ELBW) infants vocalize as early as 8 weeks before their due date, that parent talk is a significant predictor of both infant vocalizations and CTs at 32 weeks' and 36 weeks' gestation, and that ELBW infants are exposed to significantly more words from their parents than from NICU caretakers.[64] In addition, every increase in 100 adult word count (AWC)/h in the NICU at 32 weeks' gestation was associated with a 2-point increase in the BSID, Third Edition, language composite score ($P = .04$) at 18 months. Every increase in 100 AWC/h at 36 weeks' gestation was associated with a 1.2-point increase in BSID, Third Edition, cognitive composite score ($P = .004$) and a 0.3-point increase in expressive communication at 18 months ($P = .07$). This is highly suggestive that parent talk in the NICU 4 weeks and 8 weeks prior to an infant's due date has a powerful impact on subsequent infant language and cognitive development.[65]

A recent study[66] of term 3-year-old to 6-year-old children using LENA recordings and functional MRI identified that increased CTs were associated with higher parent education, higher income, higher child composite verbal scores, and bilateral MRI superior temporal lobe activation. Correlations between activation during language processing and CTs remained significant after adjustment for parent education, test scores, AWC, and child vocalizations. In a mediation model, the effect of CTs on language scores was mediated by activation of the left inferior frontal gyrus. The investigators concluded that this is the first evidence that neural activation patterns underlay

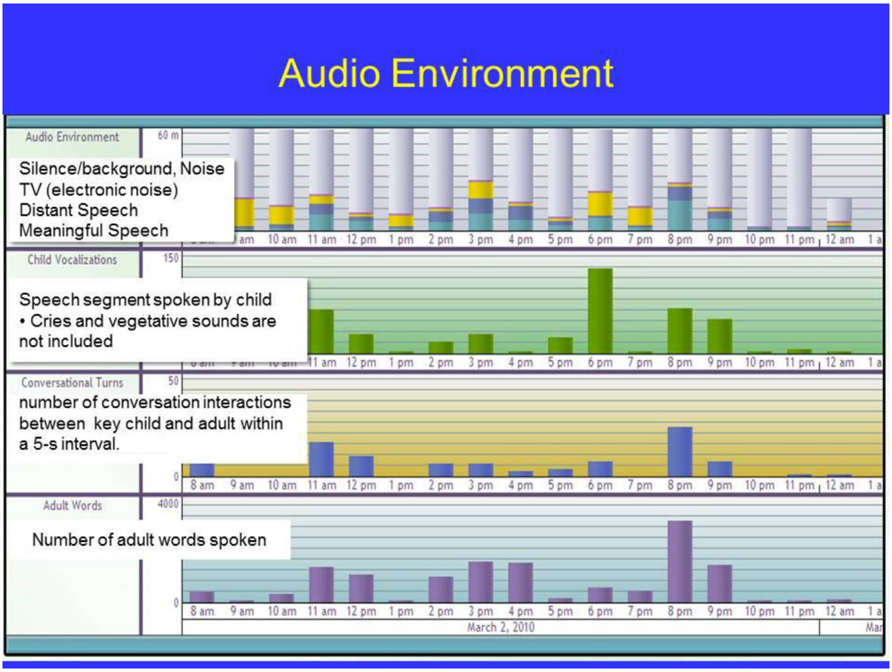

Fig. 1. Recording output.

the relationship between interactive language exposure reflected by CTs and child language abilities.[66]

These findings strongly support the concept of implementing family-integrated care[67] in the NICU and suggest that preterm infants benefit from enhanced parent presence and interaction, including caretaking, kangaroo care, cuddling, talking, singing, and reading. Open visiting and the single-room NICUs[68–70] with enhanced maternal involvement and developmental care are beneficial. Policies that remove barriers and encourage parent presence and participation in the NICU are encouraged.

SOCIOECONOMIC RISKS, MATERNAL EDUCATION LEVEL, AND BEYOND

Childhood health is closely linked to social advantage, and, typically, improvement in SES is associated with more optimal outcomes.[71–73] Measurement of social advantage or disadvantage is often difficult to capture but may include a variety of indicators, such as education status, income level, occupation, and insurance status. In the preterm population, there is evidence that both low SES and specific biologic variables are risk factors for poor developmental outcomes.[74–78] As the long-term influence of these risks is beginning to be explored, particularly in the post-surfactant era, complex interactions among these factors are becoming evident.

Current studies examining the effects of SES continue to highlight the important influence of educational status on neurodevelopmental outcomes. Linsell and colleagues,[79] in a systematic review, showed that low parental education and nonwhite race/ethnicity were predictors of pre-school (before school age, specifically 1.5 – 2.5 years of age) global impairments in VPT infants. Asztalos and colleagues,[80] of the Canadian Neonatal Follow-Up Network, reported positive association of 18-month to 21-month developmental outcomes with maternal education level. For infants born at less than 29 weeks' gestation, cognitive and language scores improved as caregiver education increased, and scores approached mean values of 100 only for infants of mothers with the highest levels of education.

The impact of parent education level seems to persist into early school years, particularly on cognitive and behavior outcomes. In a cohort of preterm infants less than 28 weeks' gestation without morbidities, such as CP, blindness, or deafness, child IQ was positively associated with higher maternal education.[81] In the EPIPAGE cohort, Beaino and colleagues[74] defined SES as both maternal and paternal education status. Low parental education was the main predictor for mild cognitive delay (adjusted odds ratio [OR] 3.43; 95% CI, 2.01–5.83) and a significant predictor for severe cognitive delay (OR 2.6; 95% CI, 1.29–5.24) at 5 years of age, along with small-for-gestational-age status and cystic periventricular leukomalacia.[74] Potharst and colleagues[82] reported on 5-year outcomes for infants less than 30 weeks' gestation, and, compared with term controls, the preterm-term mean IQ difference was 5 points, if parent education was high, and increased to 15 points, if parent education was low. Similar patterns were seen for behavior. Maternal IQ, income, occupation, and single-parent household as either independent or composite variables show similar associations with cognitive and behavior outcomes.[83–86]

As more preterm cohorts are followed longitudinally, investigators are now able to evaluate the longer-term contribution of social influences. Joseph and colleagues[87] reported that children of mothers in the lowest education stratum in the ELGAN cohort were more likely to score greater than or equal to 2 SDs below the mean on a battery of neurocognitive tests at 10 years of age. The risks of unfavorable SES, particularly in association with brain injury, have also been explored. In a European cohort of 200 ELBW infants born between 1993 and 1998, low maternal education was the most significant risk factor for decreased IQ; however, grade III/IV intraventricular hemorrhage or periventricular leukomalacia continued to have a negative impact at 13 years of age.[88] For this study, the developmental trajectories for children of mothers with higher versus lower education were different irrespective of brain injury. Children of mothers with the highest education had increases in composite IQ scores between 6 years and 13 years of age, whereas those with lower maternal education remained essentially unchanged. An Australian cohort from the same study era, comprising both early preterm/ELBW infants and normal birthweight controls,[89] reported a strong and persistent influence of intraventricular hemorrhage on cognition and academic performance at 2 years, 5 years, 8 years, and 18 years of age. Maternal education and social class, however, did not reach statistical significance until years 8 and beyond.

The interpretation of the effects of socioeconomic variables on long-term outcomes is challenging. Many adverse social situations are inter-related, tend to cluster, and have dose-response relationships with poor health.[90,91] Positive mental health is shaped by various socioeconomic and physical environments and is an integral component of enriched relationships, particularly for the mother-infant dyad. Maternal depression, anxiety, and stress have been associated with low maternal self-efficacy, defined as a mother's belief in her ability to parent.[92,93] At NICU discharge, mothers with a history of mental health disorders report decreased self-confidence compared with mothers without a history of mental health disorders.[94] Hawes and colleagues[95] report that decreased NICU discharge readiness is associated with postdischarge depressive symptoms. Importantly, within the first year of age, maternal depression and anxiety have been linked to infant dysregulation, difficult temperament, and sleep disturbances as well as compromised parent-infant interactions and inadequate parental caregiving practices.[96–99]

Less has been published on the long-term effects of maternal depression and anxiety on preterm infant outcomes; results are often conflicting and portray different patterns of symptoms.[100–102] A prospective cohort of VLBW infants born in Finland was followed from infancy to school age, and, after adjustment for maternal education level, significant associations of parental depression and stress symptoms with child cognitive, behavior, and socioemotional problems were reported between 2 years to 5 years of age.[103–105] It has been suggested that over time, parents of vulnerable infants experience increasing levels of stress. Singer and colleagues[106] reported that mothers of high-risk VLBW infants perceived increased stress extending from early childhood through adolescence compared with mothers of term or low-risk VLBW children.

It is important to recognize these long-term studies cannot determine causal pathways, because associations between parent psychological wellness and infant health/development are multifactorial and bidirectional. Mediators of maternal stress, depression, and anxiety, however, include low birthweight, low maternal education, infant and child behavior difficulties, lack of family social supports, and poor child health, all of which are more prevalent in the preterm population.[100,106–109] Additionally, the emerging field of epigenetics is beginning to uncover the effects of early adverse advents on the developing infant. One mechanism in particular, DNA methylation of genes encoding for stress regulators of the hypothalamus-pituitary-adrenal axis, shows promise.[110] In the preterm population, links between maternal anxiety and depression and alteration of infant stress-related genes have been reported, highlighting yet another pathway influencing developmental outcomes.[111–113]

In conclusion, investigations targeting psycho-socioeconomic risks provide opportunities for improving outcomes of the vulnerable preterm infant. Evidence suggests that early interventions, in particular those that focus on strengthening parent-infant relationships, have a positive influence on motor, cognitive, and behavior outcomes and may decrease parental symptoms of depression and anxiety.[38,114–116] The importance of supporting parental mental health is now widely recognized, and guidelines encourage starting this in the NICU.[117] Continued exploration of the complex interactions of psychological, social, and medical contributions is needed as efforts are made to identify effective strategies that optimize long-term outcomes for preterm infants and their families.

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