

Background

- Autism Spectrum Disorder (ASD) is a collection of neurodevelopmental disorders characterized by social-communicative and behavioral impairments that affects approximately 1 in 59 children in the US (CDC, 2018).
- Children with ASD, on average, exhibit increased rates of externalizing behaviors compared to their typically developing peers (Bauminger, Solomon, & Rogers, 2010). Studies have shown that children with relatively low familial risk for ASD are more likely to develop ASD if they have a history of prenatal complications (Dodds et al., 2011) and that history of prenatal complication is related to the severity of externalizing behaviors (DeVincent, Gadow & Tudor, 2012).
- In typical development, prenatal complications are associated with a number of child psychiatric disorders and externalizing behaviors (Allen, Lewinsohn, & Seeley, 1998; Hirshfeld Becker et al., 2004; Milberger, Biederman, Faraone, Guite, & Tsuang, 1997) and males have increased levels of externalizing behaviors compared to females (Hicks, 2008; Buil, Koot & Lier, 2017).
- The aims of the study will:
 - Compare externalizing behaviors in children with ASD who experienced prenatal complications to those children with ASD who did not experience prenatal complications.
 - Compare sex differences in externalizing behavior scores.
 - Compare externalizing behavior and sex differences in children with ASD who experienced prenatal complications to those children with ASD who did not experience prenatal complications.
- We hypothesize that:
 - ASD children with prenatal complications compared to those without complications will demonstrate more externalizing behavior problems.
 - Males with ASD will exhibit more externalizing behavior problems than female in the subscale mean scores.
 - ASD males with prenatal complications will exhibit more externalizing behavior problems.

Methods

Participants:

- Children between the ages of 8 and 17 years old participated in the Gender Exploration of Neurogenetics and Development to Advance Autism Research (GENDAAR) study. To be included in these analyses, children must (1) have a confirmed diagnoses of ASD, (2) have an IQ over 70. Mother provided information regarding whether or not she experienced pregnancy/prenatal complications with the participant child.

Table 1: Participants for Aim 1

	ASD with Prenatal Complications	ASD without Prenatal Complications
N	61 (36 males, 25 females)	106 (57 males, 49 females)
Age (Mo.)	M = 149.30, SD = 4.535	M = 150.42, SD = 3.312
Verbal IQ	M = 104.56, SD = 2.637	M = 98.40, SD = 2.012
Nonverbal IQ	M = 104.03, SD = 2.503	M = 98.46, SD = 1.647

Table 2: Participants for Aim 2

	Male ASD Children	Female ASD Children
N	74	93
Age (Mo.)	M = 149.41, SD = 3.648	M = 150.76, SD = 3.931
Verbal IQ	M = 99.46, SD = 2.183	M = 102.17, SD = 2.394
Nonverbal IQ	M = 100.54, SD = 1.846	M = 100.45, SD = 2.158

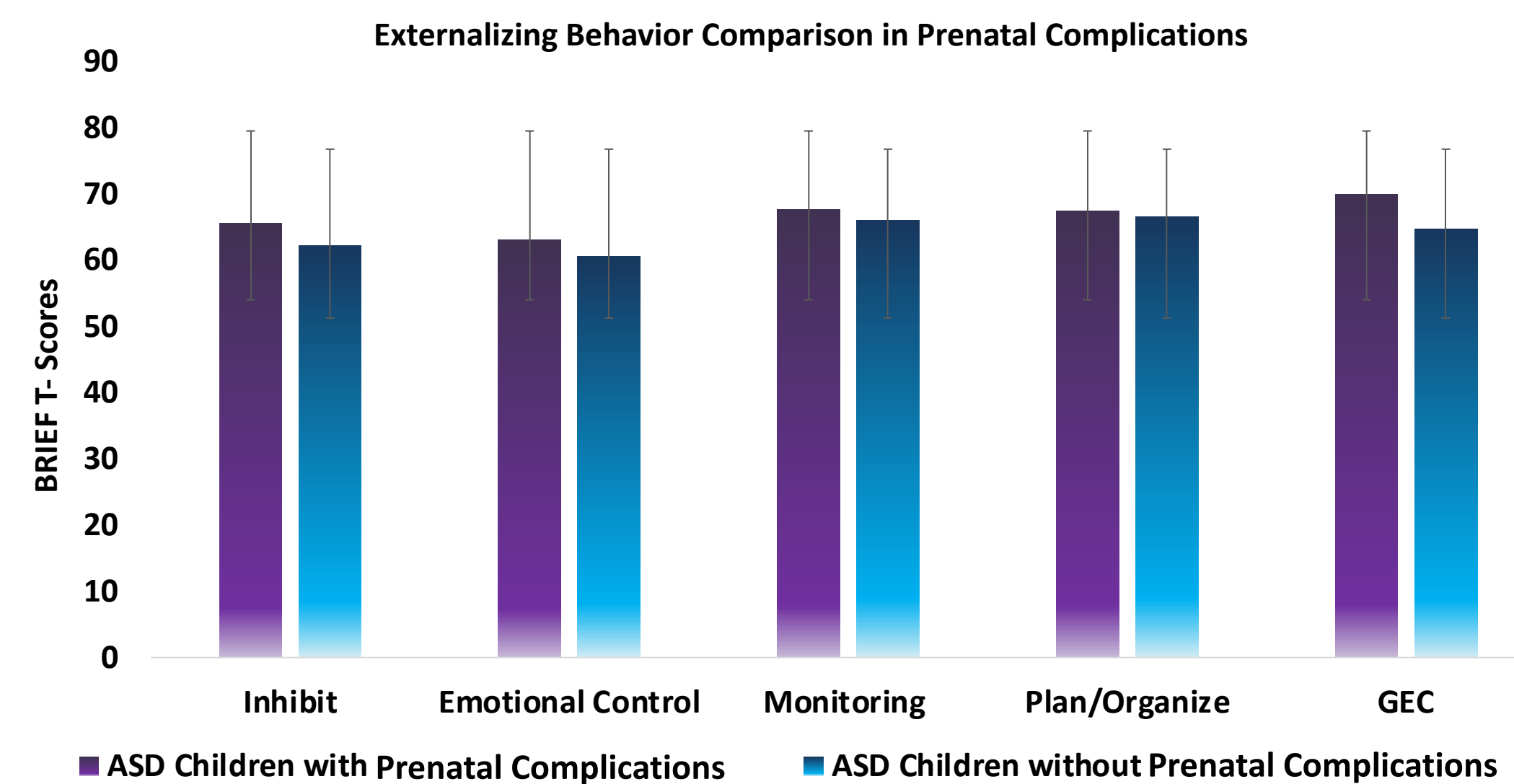
Measures:

- Pregnancy/Prenatal Complications:**
 - ACE Medical History Form:** Parent interview administered by a clinician. Includes a yes/no question regarding whether or not any prenatal complications occurred. Pregnancy/prenatal complications refers to a broad category, which includes health concerns for the mother or child, difficult birth, or coexisting pregnancy diagnosis such as gestational diabetes or preeclampsia.
- Externalizing Behaviors:**
 - Behavior Rating Inventory of Executive Functioning (BRIEF; Gioia et al., 2000):** Parent completed questionnaire assessing the child's executive function behaviors at home and at school in children and adolescents ages 5-18. Higher scores indicate more executive function problems. Provides subscale scores such as:
 - Inhibit:** Ability to control impulses (inhibitory control) and to stop engaging in a behavior.
 - Emotional Control:** Ability to regulate emotional responses appropriately.
 - Monitoring:** Ability to check work and to assess one's own performance; ability to keep track of the effect of one's own behavior on other people.
 - Plan/Organize:** Ability to anticipate future events; to set goals; to develop steps; to grasp main ideas; to organize and understand the main points in written or verbal presentations.
 - Global Executive Composite (GEC):** takes into account all of the clinical scales and represents the child's overall executive function.

Results

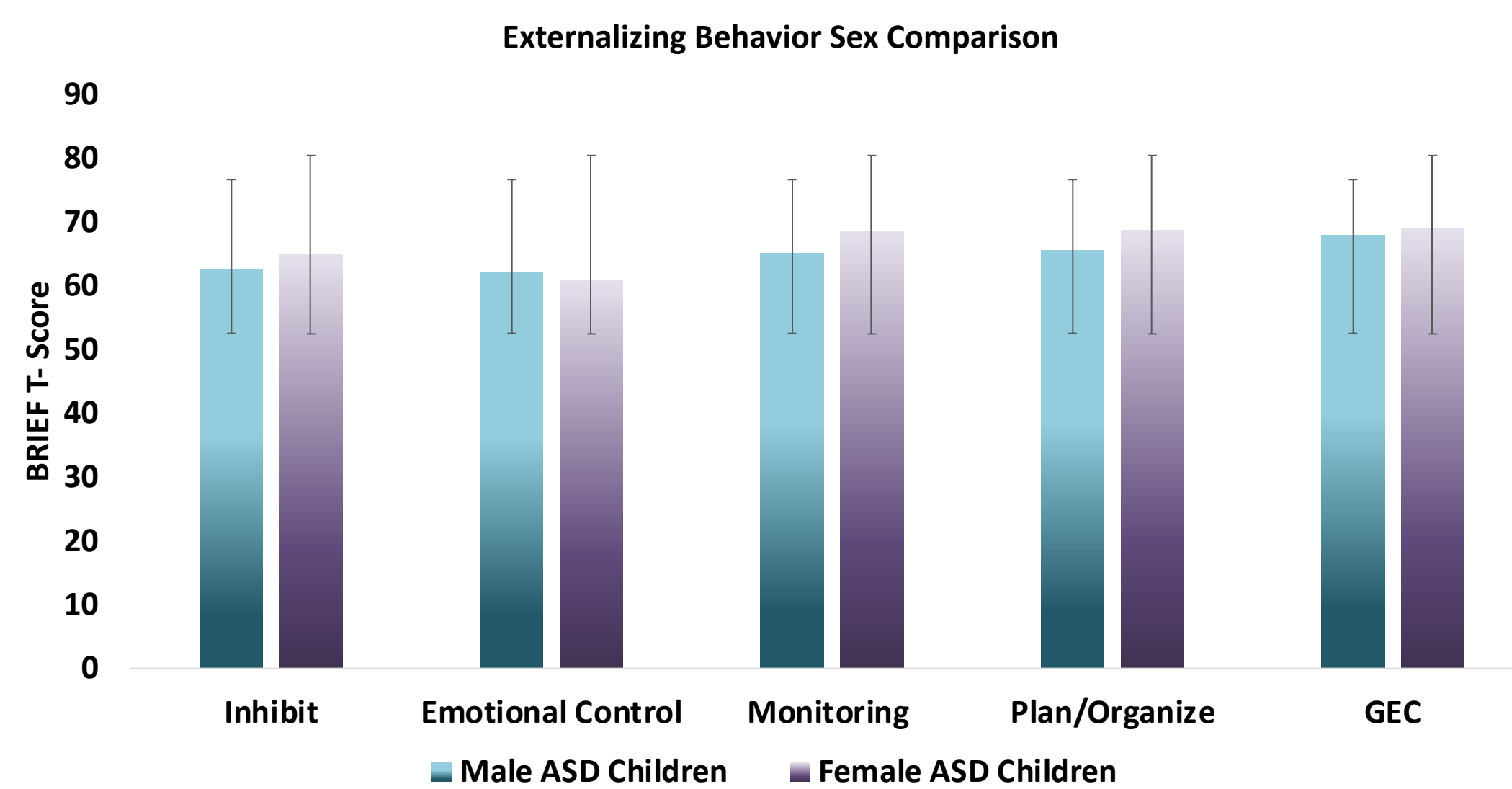
AIM 1: Comparing Externalizing Behaviors between ASD with Prenatal Complications and ASD without Prenatal Complications

- A series of ANOVAS were implemented with Inhibit, Emotional Control, Monitoring, Plan/Organize, and GEC subscales of the BRIEF as dependent variables. We found that there were **no significant differences** in any subscale between ASD children with prenatal complications and ASD children without prenatal complications.



AIM 2: Measuring Externalizing Behaviors between Male ASD children and Female ASD children

- A series of ANOVAS were implemented with Inhibit, Emotional Control, Monitoring, Plan/Organize, and GEC subscales of the BRIEF as dependent variables. We found that there were **no significant differences** in any subscale between Male ASD children and Female ASD children.



AIM 3: The Impact of Sex on the Relationship between Prenatal Complications and Externalizing Behaviors

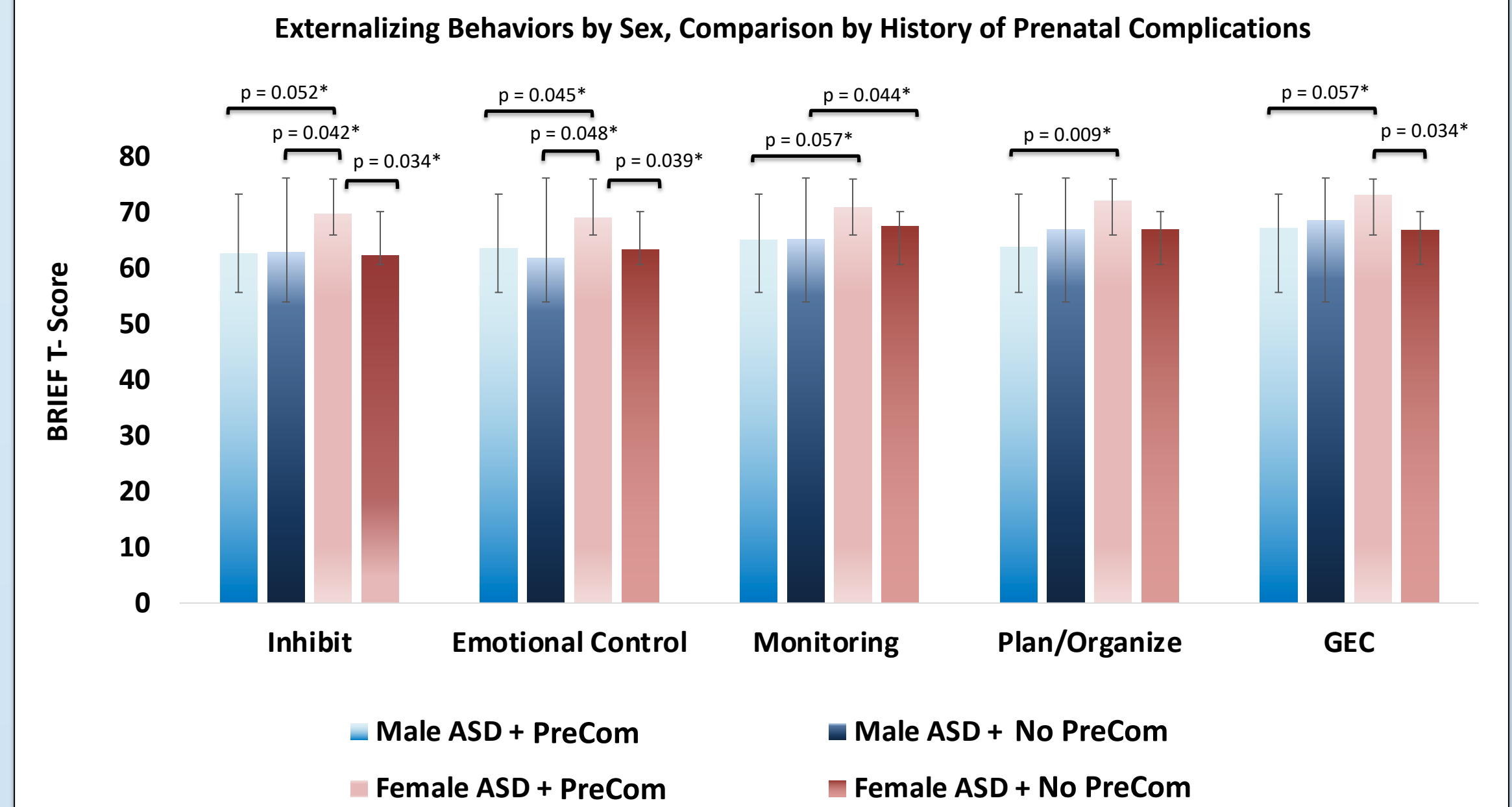
- To perform this analysis, we categorized the participants in four groups: Male ASD with prenatal complications, Male ASD without prenatal complications, Female ASD with prenatal complications, and Female ASD without prenatal complications.

Table 3: Descriptive values on Age and IQ for each group.

	Male ASD with Prenatal Complications	Male ASD w/o Prenatal Complications	Female ASD with Prenatal Complications	Female ASD w/o Prenatal Complications
N	36	57	25	49
Age (Mo.)	M = 150.25, SD = 5.837	M = 148.25, SD = 4.828	M = 146.48, SD = 7.805	M = 152.94, SD = 4.706
Verbal IQ	M = 106.25, SD = 3.414	M = 95.18, SD = 2.746	M = 102.12, SD = 4.239	M = 102.14, SD = 3.026
Nonverbal IQ	M = 105.50, SD = 2.989	M = 96.77, SD = 2.176	M = 100.48, SD = 4.195	M = 100.43, SD = 2.628

- A series of ANOVAS were implemented with Inhibit, Emotional Control, Monitoring, Plan/Organize, and GEC subscales as dependent variables. We found that there were **significant differences**, across all subscales, between the four groups.

AIM 3: Comparing Externalizing Behaviors for Males and Females with ASD, with and without Prenatal Complications.



- We found that female ASD children with prenatal complications **scored significantly higher (worse)** on BRIEF subscale measures of Inhibit (p=0.052), Emotional Control (p=0.045), & Plan/Organize (p=0.009) and **scored marginally higher (worse)** on BRIEF subscale measures of: Monitoring (p=0.057) & GEC (p=0.057) compared to male ASD children with prenatal complications.
- Furthermore, female ASD children with prenatal complications **scored significantly higher (worse)** on BRIEF subscale measures of Inhibit (p=0.034), Emotional Control (p=0.039) and GEC (p=0.034) compared to female ASD children without prenatal complications.
- Lastly, we found that female ASD children without prenatal complications **scored significantly higher (worse)** on BRIEF subscale measures of Monitoring (p=0.044) compared to male ASD children without prenatal complications.

Discussion

Summary:

- Overall, there were **no significant differences** on externalizing behaviors, in any subscales, when comparing children with ASD with or without prenatal complications or when comparing children with ASD by sex. This does not support my first and second hypotheses.
- However, when taking into account both prenatal complication and sex together, female ASD children with prenatal complications **demonstrate more externalizing behaviors** compared to all three other groups. This finding did not support my third hypothesis.

Caveats:

- It is important to note that this study differs from other studies because it included only children with functional language and average to above average IQ. Furthermore, it also included a larger percentage of females with ASD.
- Prenatal complications may not have been as severe as in previous reports because we excluded any participants that had experience severe prenatal complications.

Discussion

- In conclusion, pregnancy/prenatal complications may impact males and females with autism differently. The fact that we found differences in this population with strict limitations of our pregnancy complications being relatively minor is worth noting.
- However, these results do align with previous research showing a relationship between: fetal sex → pregnancy/prenatal complications → externalizing behaviors. Follow up studies should include both higher rates of females with ASD and minor prenatal complications.
 - Other reports show that rates of hypertensive disorders, especially preeclampsia and pregnancy-induced hypertension (PIH), may be higher in pregnant women carrying female fetuses compared to those carrying male fetuses due to higher levels of spermine metabolites (Shiozaki et al., 2011; Gong et al., 2018).
 - Spermine synthase expresses a spermine metabolite called N1,N12-diacetyl spermine which was found to escape X-chromosome inactivation. As a result, it causes higher expression in female placentas and serum.
 - Furthermore, there have been studies that linked fetal exposure to preeclampsia with worsening externalizing behaviors and trigger aberrant neurodevelopment in fetuses (Robinson et al., 2009; Walker et al., 2015; Dachew et al., 2018).

Conclusions & Limitations:

- These findings emphasize the role of sex and prenatal complications in externalizing behaviors.