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Prenatal Depression and Risk of Child Autism-related Traits Among Participants in the Environmental influences on Child Health Outcomes (ECHO) Program

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Abstract

This study evaluated the association between prenatal depression and offspring autism-related traits. The sample comprised 33 prenatal/pediatric cohorts participating in the Environmental influences on Child Health Outcomes (ECHO) program who contributed information on prenatal depression and autism-related traits. Autism-related traits were assessed continuously and at the diagnostic cut-off using the Social Responsiveness Scale (SRS) for children up to 12 years of age. Main analyses included 3,994 parent-child pairs with prenatal depression diagnoses data; secondary analyses included 1,730 parent-child pairs with depression severity. After confounder adjustment, we observed an increase in autism-related traits among children of individuals with prenatal depression compared to those without (adjusted β = 1.31 95% CI: 0.65, 1.98). Analyses stratified by child sex documented a similar significant association among boys (aβ = 1.34 95%CI: 0.36, 2.32) and girls (aβ = 1.26 95% CI: 0.37, 2.15). Prenatal depression was also associated with increased odds of moderate to severe autism-related traits (adjusted Odds Ratio: 1.64, 95%CI: 1.09, 2.46), the screening threshold considered high risk of ASD diagnosis. Findings highlight the importance of prenatal depression screening and preventive interventions for children of pregnant individuals with depression to support healthy development. Future research is needed to clarify whether these findings reflect overlap in genetic risk for depression and ASD-related traits or another mechanism.

Lay Summary:

Prenatal depression was associated with an increase in autism-related traits and increased risk of moderate-to-severe autism-related traits, the screening threshold considered at high risk for an ASD diagnosis. Findings highlight the importance of prenatal depression screening and preventive interventions for children of pregnant individuals with depression to support healthy development. Future research is needed to clarify whether these findings reflect overlap in genetic risk for depression and ASD-related traits or another mechanism.

Keywords

Autism Spectrum Disorder; depression; pregnancy; parent-child relations; male; female

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition that presents along a continuum of deficits in social communication, sensory processing, and repetitive behaviors that usually persist into adulthood. The prevalence of ASD has been increasing over the past few decades, with recent reports documenting a prevalence of 1 in 44 among 8-year-old children, and a four-fold higher prevalence in boys than girls.(Maenner MJ et al., 2021) There is a growing consensus that the etiology of ASD is complex and includes prenatal origins.(Lyall et al., 2017)

A growing body of epidemiologic research suggests an association between prenatal depression(Chen et al., 2020; Hagberg et al., 2018),(El Marroun et al., 2014) or a history of depression any time prior to conception(Rai et al., 2013; Wieckowski et al., 2017; Wiggins

et al., 2019) and ASD. These reports compose a small subset of papers in the sizable literature linking prenatal distress (including affective symptoms and stress) with many features of child neurodevelopment.(O'Donnell et al., 2017; Qiu et al., 2015; Robinson et al., 2022) Yet, much of the literature has focused on ASD diagnoses with only one study evaluating autism-related traits.(El Marroun et al., 2014) While this study identified an association between higher prenatal depressive symptomology and child autistic-related traits, it lacked data on prenatal depression diagnoses. Further, the study did not evaluate sex-specific associations.

The examination of social communication and other autism-related traits is consequential for a greater understanding about the extent to which prenatal depression may affect attributes that do not meet the threshold of an ASD diagnosis. This knowledge is especially critical given the association of autism-related traits such as social communication and behavioral attributes, regardless of whether they reach the threshold for a clinical diagnosis, with impairments in children's physical, social and psychological development.(DL & JC, 2002)

To address these gaps in the literature we identified pregnant individuals participating in the Environmental influences on Child Health Outcomes (ECHO) program with follow-up data on children up to age 12. In the present study, we examined the association between prenatal depression defined by diagnoses and symptom severity and child autism-related traits as assessed using the Social Responsiveness Scale (SRS). We also examined whether this association varied for boys compared to girls.

Methods

Data source and analytic cohorts

This analysis was conducted using data from the ECHO program, a National Institute of Health-funded national consortium of 69 prenatal and pediatric cohorts with substantial demographic and geographic heterogeneity.(Gillman & Blaisdell, 2018) The ECHO consortium systematically collects information on child risk behaviors, health and well-being from longitudinal child health cohort studies from across the US to assess how early-life environmental exposures influence key domains of child health including neurodevelopment.(Blaisdell et al., 2021) Information regarding the ECHO data collection protocol has been previously described. (Knapp et al., 2023)

The institutional review boards of each cohort site as well as the host institutions of the ECHO components reviewed and approved the activities of this study.

The parent-child dyads included in this analysis were restricted to the following: 1) availability of data on the relevant exposure (see details below) and the outcome, 2) no reported use of antidepressant medications during pregnancy, and 3) the SRS was assessed in the child using the preschool SRS form (ages 2.5 – 4.5 years) or the school-age SRS form (ages 4 – 12 years).

A total of 33 cohorts (including 1 autism-enriched cohort) contributed parent-child data (N=5,553) to at least one analysis. Only the first parent-child dyad for each birthing parent

with more than one child during the study period was included to avoid non-independence. Cohorts that contributed <10 parent-child dyads were excluded. Additionally, given that preterm birth is a strong risk factor for ASD and the limited generalizability of cohorts that enrolled only preterm infants, cohorts that enrolled only preterm infants were excluded. Data were collected between 2007–2022.

Exposures

Prenatal depression was defined in two ways. Our primary prenatal depression exposure was defined as a depression diagnosis during pregnancy captured by either self-report (n=734) or medical records (N= 3,260, total N=3,994). Data from biological mothers on presence or absence of a diagnosis of depression (International Classification of Diseases (ICD-9): 296.2X, 296.3X, 300.4, 296.9X; ICD-10: f32.XX, F33.XX, F34.1, F39.XX) from 4 weeks prior to the reported last menstrual period prior to pregnancy through 8 weeks postpartum were included in the depression diagnosis during pregnancy analysis.

Secondary analyses were conducted using prenatal depression severity defined using the ECHO harmonized PROMIS T-score(Blackwell et al., 2018) metric during pregnancy. Individuals who completed the PROMIS-D or any of the depression screeners listed below during pregnancy were included (N=1,730). Harmonization to the PROMIS Depression used state-of-the-science PROsetta Stone® score-linking methodology(Choi et al., 2021), which uses item response theory and equipercentile score-linking to enable conversion of legacy measure scores to the PROMIS Depression T-score (mean = 50, SD = 10), which is normed to the general US population. The PROMIS depression item bank consists of 28-items scored on a 5-point Likert scale focused on cognitive and emotional manifestations of depression over the past week. An 8-item short form generated from the larger question bank has also been validated. In addition, scores from 4 additional measures (Edinburgh Postnatal Depression Scale (EPDS),(Cox et al., 1987), Brief Symptom Inventory (BSI), (Derogatis, 2001) Center for Epidemiologic Studies Depression Scale (CESD),(Lewinsohn et al., 1997) and the Patient Health Questionnaire (PHQ9),(Manea et al., 2012) were cross-walked to the PROMIS T-score metric and harmonized for use across ECHO. Validation of these harmonization efforts is documented elsewhere.(Blackwell et al., 2021; Choi et al., 2014; Kaat et al., 2017; Tang et al., 2022) The mean PROMIS T-scores for the individual cohorts ranged from 43.8 – 58.6. Prenatal depression severity was assessed in two ways: 1) Continuous T-Score, and 2) Categorized into 3 groups (≤59.9 [mild-moderate depression] as the reference, ≥60.0 – 65.8 as moderately-severe, and ≥65.9 as severe depression).(Pilkonis et al., 2014) Separate analyses were conducted using these two exposure definitions.

Outcome

Autism-related traits.—The Social Responsiveness Scale (SRS) was used to evaluate autism-related traits. The validated SRS(Constantino et al., 2009; Constantino et al., 2003) is a well-established 65 item scale used to identify the presence and severity of social impairment symptoms within the autism spectrum. It was designed for use in both autism-affected and general populations(Constantino, 2012; Constantino & Todd, 2003) and is completed by the parent or caregiver. Each item on the scale is rated from 0 (never true) to 3 (almost always true) and the total raw score ranges from 0 to 195. The preschool form

was used for ages 2.5–4.5 years; and the school-aged form was used for children aged 4–12 years. The overlap in age ranges allowed for variability in developmental stage. SRS total raw scores from the preschool and school-aged versions of the SRS were converted to sex-normed T-scores (mean = 50, standard deviation = 10) to facilitate clinical utility. The mean SRS score for each individual cohort in the analysis ranged from 41.9 – 61.5. The SRS T-scores were used to assess ASD-related traits on a continuous scale. Higher scores indicate greater expression of the ASD-related phenotype and greater social-communication deficits. (Constantino, 2013; Constantino, 2012) We also conducted analyses with dichotomized SRS scores to distinguish moderate-to-severe (SRS T-score: ≥66) from mild (SRS T-score: <66) autism-related traits. Scores above ≥66 are correlated with an ASD diagnosis.(Constantino, 2013; Constantino, 2012)

Covariates

Covariates were ascertained through a combination of self-report and medical record review. Prenatal tobacco use and alcohol use were dichotomized as “any” vs. “none”. Education was categorized as “high school degree/GED or less”, “some college”, vs. “Bachelor’s degree and above”. Maternal race was defined as “White”, “Black” and “Other” and Ethnicity was defined as “Non-Hispanic”, “Hispanic”. Pre-pregnancy body mass index (BMI; kg/m^2) was calculated using the weight between 12 months prior to pregnancy through the end of the first trimester closest to conception and included in the analysis as a continuous variable. Child age at SRS ascertainment was included as a continuous variable. Child sex was dichotomized as “male” vs. “female” based on assigned biological sex at birth. Variables potentially on the causal pathway (e.g., preterm delivery) were not included as covariates.

Statistical Analysis

A directed acyclic graph (DAG) was used to inform the analysis. Covariates included in the DAG were based on conceptual and empirical justification from the existing literature as being associated with prenatal depression and childhood social impairment. Missing data on various maternal covariates including age at delivery (<0.1%), education (4.6%), race (3.9%), ethnicity (0.8%), marital status (41.3%), pre-pregnancy BMI (4.7%), prenatal alcohol use (5.2%), and prenatal tobacco use (0.7%) (Table 1) were imputed using the Multivariate Imputation by Chained Imputation (MICE) package in R,(Zhang, 2016) with all other variables from the analytic models included as predictors. Results were pooled after 25 iterations.(Raghunathan et al., 2002)

We employed linear mixed effects models with cohort as a random effect to examine the associations between each exposure and the outcome. Associations between prenatal depression and SRS scores were examined in multiple ways for a greater understanding of potential associations. The first model assessed prenatal depression diagnosis (primary exposure) as a binary exposure in relation to SRS T-scores. To explore sex as an effect modifier in the primary model, we stratified by sex and also tested an interaction term between sex and depression in the primary model evaluating prenatal depression diagnoses and SRS T-scores. A sensitivity analysis was conducted using a mixed-effects logistic regression model with cohort as a random effect to evaluate prenatal depression diagnosis in relation to the categorized SRS T-score outcome (≥66 vs. <66) to understand whether

prenatal depression influences social communication deficits at scores generally consistent with an ASD diagnosis.

Secondary analyses were conducted to understand associations between child outcome and maternal depressive symptom severity using the PROMIS depression T-score, modeled as either a continuous exposure measure or categorized into three levels based on cut points of mild, moderate, and severe depressive symptoms. Sensitivity analyses modeled the association of both measures of depressive symptom severity and the dichotomous SRS T-score of <66 vs ≥66. Further, additional sensitivity analyses were conducted restricting the sample with depression diagnoses to include only those identified by the electronic health record (EHR). All analyses were conducted using R Version 4.1.0 in a secure virtual private network platform hosted by the Research Triangle Institute (RTI) using de-identified data.

Results

Prenatal Depression Diagnosis

The sample to evaluate the primary exposure of prenatal depression diagnosis included 3,994 parent-child pairs. Characteristics of the study population overall and by prenatal depression status are documented in Table 1. Overall, a majority of the pregnant individuals was White (75.1%), 5.2% Black, and 14.1% Hispanic. The sample was more likely to have a bachelor's or higher degree (59.5%) than not, and the mean (SD) age at delivery was 30.8 (5.14) years. There were some demographic differences between individuals with a prenatal depression diagnosis and without, including that those with a prenatal depression diagnosis had a higher mean pre-pregnancy BMI (28.3 SD (7.29) vs. 26.3, SD (6.09), $p<0.01$), were more likely to smoke during pregnancy (13.1% vs. 6.3%, $p<0.01$) and less likely to have a bachelor's degree or higher (46.0% vs. 62.0%, $p<0.01$). The mean age for the child's SRS screener was 5.37 (SD 2.47), the mean (SD) population SRS score for the preschool form was 44.2 (6.55) and school-aged form was 49.4 (9.27), and 95.6% of the children (n=3,818) scored <66. Characteristics of the sample stratified by ASD-Enriched Cohort and non-ASD Enriched Cohorts are presented in Supplemental Table 1.

After adjusting for confounders, we observed that SRS T-scores were on average 1.31 points higher (i.e., greater autism-related traits) among children of individuals with prenatal depression compared with those without depression (95% CI: 0.65, 1.98) (Table 2)

Analyses stratified by child sex documented a significant association among boys ($\beta = 1.34$ 95% CI: 0.36, 2.32) and girls ($\beta = 1.26$ 95% CI: 0.37, 2.15); there were no significant sex-based differences in the strengths of these associations (interaction p=0.92). Analyses of dichotomized SRS T-scores demonstrated a statistically significant increased odds of moderate-to-severe autism-related traits in children of individuals with prenatal depression compared to those without (aOR: 1.64, 95% CI: 1.09, 2.46), after adjusting for potential confounders (Table 3).

Sensitivity analyses restricting the sample to individuals in which prenatal depression diagnoses were based on EHR data and restricting to the non-ASD enriched cohorts produced similar, if not slightly stronger results (Supplemental Tables 2–5).

Prenatal Depression Severity

In the sample of maternal-child dyads with prenatal depressive symptom severity data (n=1730, Supplemental Table 6), every unit increase in the depression severity T-score was associated with a 0.21 standard deviation increase in autism-related traits (β = 0.21 95% CI: 0.15, 0.27) after adjustment for covariates (Table 2). Sensitivity analyses examining dichotomized SRS T-scores (aOR: 1.07 95% CI: 1.04, 1.11; Table 3) demonstrated similar results. Analyses categorizing depressive symptom severity suggest a positive dose-response association between prenatal depressive symptom severity and autism-related traits; compared to mild depressive symptoms, moderate depression severity was associated with a 2.65 T-score unit increase (95% CI: 1.09, 4.22) in SRS T-scores and severe depression severity was associated with a 4.96 T-score unit increase (95% CI: 1.86, 8.05) compared to mild depressive symptoms. A somewhat similar association was noted in the odds of moderate-to-severe autism-related traits (moderate: aOR: 3.02, 95% CI: 1.64, 5.59 and severe: aOR: 3.40, 95%CI: 1.06, 10.93 compared to mild depression symptoms) (Tables 2 and 3, respectively).

Discussion

These findings from the national ECHO study demonstrate a positive association between prenatal depression and children's ASD-related traits. Additional analyses confirmed the magnitude of the association escalated with increasing depression severity. The relationship between prenatal depression diagnosis and ASD-related traits was similar for boys and girls. Further, we found prenatal depression associated with an increased risk for child SRS scores above the threshold that correlates with an ASD diagnosis. This study adds a broader understanding of the association between prenatal depression and ASD, demonstrating an association with deficits in social communication and behavioral characteristics that may not reach a clinical threshold, yet can impact social and behavioral functioning. Further, findings from this study provide data for more informed clinical decisions for treating prenatal depression.

To our knowledge the relationship between prenatal depression and ASD-related traits in the offspring has only been investigated in one study which reported an association between high depressive symptoms and a modest increase in ASD-related traits.(El Marroun et al., 2014) This prior study used data from the Generation R study of pregnant residents in Rotterdam and included a much smaller sample of women with prenatal depression. These findings are consistent with our study that similarly found prenatal depression severity as well as well as depression diagnoses associated with increasing ASD-related traits. Little, if any attention has been given to variations in associations between prenatal depression and ASD or ASD-related traits by child sex. Although our tests of moderation by child sex were not statistically significant, larger sample sizes are likely needed to discern whether associations are sex-specific.

There are multiple plausible mechanisms through which prenatal depression may impact child ASD risk. Suggesting a possible direct relationship, high *in utero* cortisol levels associated with prenatal depression may adversely affect the offspring.(Alder et al., 2007; Bao et al., 2007; Chrousos et al., 1998; Kalantaridou et al., 2004; Mastorakos & Ilias,

2000, 2003; Mastorakos et al., 2006; Vitoratos et al., 2006) Elevated *in utero* cortisol levels have been linked to abnormal child amygdala volume (a characteristic of children with autism)(Schumann et al., 2009) with sex-specific differences.(Buss et al., 2012) Further, increased *in utero* cortisol concentrations may also induce vasal constriction in the placenta resulting in hypoxic injury and subsequent significant structural and functional brain injuries in the offspring.(Field et al., 2006; Kinsella & Monk, 2009) Genetic factors have also been hypothesized to play a role in the etiology of ASD in the offspring. For example, serotonergic disruption is characteristic of both prenatal depression and ASD. Serotonin (5-HT) is an important neurotransmitter in mood regulation and diminished levels are associated with depression. Atypical serotonergic pathways have also been noted in individuals with ASD(Anderson et al., 2009; Pardo & Eberhart, 2007), thus suggesting a potential common genetic pathway. Additionally, genome-wide association studies have identified common genetic risk variants between ASD and depression.(Morimoto et al., 2021) Future research is needed to clarify whether our findings reflect a genetic risk for depression and ASD-related traits or another underlying mechanism.

Strengths and Limitations

The findings from this study should be considered in the context of its limitations. First, outcome misclassification is a possibility, however the SRS is a validated and widely used instrument for evaluating autism-related traits.(Constantino et al., 2009; Constantino et al., 2003; Constantino & Todd, 2003) Some of the data were captured through self-report or parent report and we were not able to evaluate associations with timing of prenatal depression or symptom severity during pregnancy. We were not able to assess potential bias in parental reporting of their children's social responsiveness due to parental depression post pregnancy. Additionally, although we were interested in the relationship of untreated prenatal depression on autism-related traits and we excluded parent-infant pairs with evidence of prenatal antidepressant exposure, we did not have information on prenatal antidepressant exposure on all individuals in the sample. Thus, it is possible that the findings may be partially attributed to antidepressant exposure. However, a recent systematic review concluded that research documenting associations between *in utero* antidepressant exposure and child ASD is likely due to confounding by indication, or the underlying depression. (Morales et al., 2018) It is possible that ascertainment of depression from the electronic health records missed diagnoses for those with more chronic depression with a diagnosis indicated earlier than 4 weeks prior to pregnancy. However, any exposure misclassification would be non-differential and thus our current findings would actually be an underestimate of the true association. Overall, we had low levels of missingness, except for marital status. To address this, we conducted Multivariate Imputation by Chained Imputation (MICE) using a large number of predictor variables. We do not have data on parental autism-related traits which may be associated with both parental depression as well as autism-related traits in the child. Future research should ascertain this information to assess the covariance of prenatal depression and parental autism-related traits on child development. Finally, the study may not be generalizable to pregnant individuals with more severe depression taking antidepressant medications.

There are many strengths to the study including the large, racial and ethnic and geographic diversity of the cohort. While most studies to date have been limited to autism diagnoses, we evaluated a continuous measure of autism-related traits, that allowed us to capture more subtle relationships with latent traits and subclinical manifestations of autism. Additionally, the assessment of both depression diagnoses and depression severity in pregnant individuals not taking antidepressant medications addresses confounding by indication which is a methodological limitation of previous research.

Conclusions

Overall, findings suggest a positive association between prenatal depression diagnosis and symptom severity and an increased risk of autism-related traits of the offspring. Future research incorporating parent and child genetic data is needed to clarify whether these findings reflect overlap in genetic risk for depression and ASD-related traits or another mechanism. These findings suggest the importance of screening for children of individuals who had prenatal depression in the months and years after birth to promote early intervention and support healthy development. Additionally, mental health screening and preventive interventions for depression in pregnant individuals may also provide benefits.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

De-identified data from the ECHO Program are available through NICHD's Data and Specimen Hub (DASH): https://dash.nichd.nih.gov/. DASH is a centralized resource that allows researchers to access data from various studies via a controlled-access mechanism. Researchers can now request access to these data by creating a DASH account and submitting a Data Request Form. The NICHD DASH Data Access Committee will review the request and provide a response in approximately two to three weeks. Once granted access, researchers will be able to use the data for three years. See the DASH Tutorial for more detailed information on the process: https://dash.nichd.nih.gov/resource/tutorial .

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Table 1.

Demographic Characteristics of the 3994 Parent-Child Dyads Participating in ECHO with Child Birthdates between 2004–2020, Overall and by Prenatal Depression * Status

	Overall (N=3994)	Prenatal Depression (N=635)	No Prenatal Depression (N=3359)	p-value
BIRTHING PARENT CHARACTERISTICS				
Prenatal Depression Source				
Medical Record	3260 (81.6%)	585 (92.1%)	2675 (79.6%)	<0.01
Self-Report	734 (18.4%)	50 (7.9%)	684 (20.4%)	
Age at Delivery				
Mean (SD)	30.8 (5.14)	30.7 (5.65)	30.9 (5.03)	0.3891
Median [Min, Max]	31.0 [14.0, 47.0]	31.0 [15.0, 45.0]	31.0 [14.0, 47.0]	
Missing	<5	0 (0%)	<5	
Education				
High school degree or less	408 (10.2%)	89 (14.0%)	319 (9.5%)	<0.01
Some college, Trade school	1027 (25.7%)	214 (33.7%)	813 (24.2%)	
Bachelor's degree and above	2376 (59.5%)	292 (46.0%)	2084 (62.0%)	
Missing	183 (4.6%)	40 (6.3%)	143 (4.3%)	
Race				
White	2998 (75.1%)	472 (74.3%)	2526 (75.2%)	0.984
Black	209 (5.2%)	32 (5.0%)	177 (5.3%)	
Other	632 (15.8%)	100 (15.7%)	532 (15.8%)	
Missing	155 (3.9%)	31 (4.9%)	124 (3.7%)	
Ethnicity				
Non-Hispanic	3402 (85.2%)	515 (81.1%)	2887 (85.9%)	<0.01
Hispanic	562 (14.1%)	113 (17.8%)	449 (13.4%)	
Missing	30 (0.8%)	7 (1.1%)	23 (0.7%)	
Marital Status				
Married/Living with a partner	1993 (49.9%)	266 (41.9%)	1727 (51.4%)	<0.01
Not Married	352 (8.8%)	70 (11.0%)	282 (8.4%)	
Missing	1649 (41.3%)	299 (47.1%)	1350 (40.2%)	
Pre-pregnancy BMI (kg/m^2)				
Mean (SD)	26.6 (6.34)	28.3 (7.29)	26.3 (6.09)	<0.01
Median [Min, Max]	24.9 [15.5, 63.8]	26.6 [16.4, 58.8]	24.7 [15.5, 63.8]	
Missing	189 (4.7%)	28 (4.4%)	161 (4.8%)	
Prenatal Alcohol Use				
No	2753 (68.9%)	401 (63.1%)	2352 (70.0%)	<0.01
Yes	1035 (25.9%)	192 (30.2%)	843 (25.1%)	
Missing	206 (5.2%)	42 (6.6%)	164 (4.9%)	
Prenatal Tobacco Use				
No	3674 (92.0%)	546 (86.0%)	3128 (93.1%)	<0.01
Yes	294 (7.4%)	83 (13.1%)	211 (6.3%)	

	Overall (N=3994)	Prenatal Depression (N=635)	No Prenatal Depression (N=3359)	p-value
Missing	26 (0.7%)	6 (0.9%)	20 (0.6%)	
Parity				
0	1646 (41.2%)	255 (40.2%)	1391 (41.4%)	0.5246
1	1376 (34.5%)	216 (34.0%)	1160 (34.5%)	
2+	916 (22.9%)	157 (24.7%)	759 (22.6%)	
Missing	56 (1.4%)	7 (1.1%)	49 (1.5%)	
CHILD CHARACTERISTICS				
Sex of the Child				
Male	2084 (52.2%)	321 (50.6%)	1763 (52.5%)	0.3944
Female	1910 (47.8%)	314 (49.4%)	1596 (47.5%)	
Age of Child at SRS Screener				
Mean (SD)	5.37 (2.47)	5.66 (2.64)	5.31 (2.44)	<0.01
Median [Min, Max]	4.58 [2.50, 12.0]	4.70 [2.58, 12.0]	4.56 [2.50, 12.0]	
SRS Total T-score				
Mean (SD)	47.6 (8.77)	49.3 (9.51)	47.2 (8.59)	<0.01
Median [Min, Max]	46.0 [34.0, 102]	47.0 [34.0, 94.0]	45.0 [34.0, 102]	
Dichotomized SRS Total T-score				
None/Mild symptoms (<66)	3818 (95.6%)	592 (93.2%)	3226 (96.0%)	<0.01
Moderate/Severe symptoms (≥66)	176 (4.4%)	43 (6.8%)	133 (4.0%)	
Child Year of Birth				
2004–2009	358 (9.0%)	75 (11.8%)	283 (8.4%)	<0.01
2010–2020	3636 (91.0%)	560 (88.2%)	3076 (91.6%)	

Note: Exact numbers and percentages are not given for small cells to minimize risk of violation of confidentiality

* Prenatal depression defined by a combination of self-report and diagnoses ascertained from medical records.

Table 2.

The Associations between Prenatal Depression and Depression Severity with Autism-related Traits (T-Score)

	Crude β*	95% CI	Adjusted β**	95% CI
Prenatal Depression Diagnosis (Binary)				
Overall	1.90	(1.22, 2.57)	1.31	(0.65, 1.98)
Male	1.84	(0.84, 2.83)	1.34	(0.36, 2.32)
Female	1.94	(1.04, 2.84)	1.26	(0.37, 2.15)
Prenatal Depression Severity (Continuous)				
Overall	0.25	(0.19, 0.31)	0.21	(0.15, 0.27)
Prenatal Depression Severity (Categorical)				
No/Mild depression symptoms (≤59.9)	REF		REF	
Moderate (60.0–65.8)	3.32	(1.72, 4.93)	2.65	(1.09, 4.22)
Severe (≥65.9)	5.97	(2.82, 9.11)	4.96	(1.86, 8.05)

Note: Depression diagnoses defined by self-report or medical records; depression severity assessed by the PROMIS T-score (continuous and by three categories); Autism-related traits assessed by continuous SRS T-score

*ECHO cohort included as a random effect in the model

**adjusted for ECHO cohort as a random effect, prenatal alcohol use, prenatal tobacco use, pre-pregnancy BMI (kg/m^2), birthing parent education, race and ethnicity, age at delivery and marital status, child age at SRS and sex; stratified models not adjusted for child sex

Table 3.

Sensitivity Analyses: Odds Ratios for the Associations Between Prenatal Depression and Depression Severity with Moderate/Severe Autism-related Traits

	Crude OR*	95% CI	Adjusted OR**	95% CI
Prenatal Depression Diagnosis (Binary)				
Overall	1.95	(1.31, 2.90)	1.64	(1.09, 2.46)
Prenatal Depression Severity (Continuous)				
Overall	1.07	(1.04, 1.10)	1.07	(1.04, 1.11)
Prenatal Depression Severity (Categorical)				
No/Mild depression symptoms (≤59.9)	REF		REF	
Moderate (60.0–65.8)	2.96	(1.65, 5.31)	3.02	(1.64, 5.59)
Severe (≥65.9)	3.28	(1.10, 9.80)	3.40	(1.06, 10.93)

Note: Depression diagnoses defined by self-report or medical records; depression severity assessed by the PROMIS T-score (continuous and by three categories); Autism-related traits assessed by dichotomized SRS T-score (≥66 vs. <66)

* ECHO cohort included as a random effect in the model

** adjusted for ECHO cohort as a random effect, prenatal alcohol use, prenatal tobacco use, pre-pregnancy BMI (kg/m^2), birthing parent education, race and ethnicity, age at delivery, marital status, child age at SRS and sex.