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Prenatal Antidepressant Exposures and Autism Spectrum Disorder or Traits: A Retrospective, Multi-Cohort Study

Patricia A. Brennan[1], **Anne L. Dunlop**[2], **Lisa A. Croen**[3], **Lyndsay A. Avalos**[3], **Amy L. Salisbury**[4], **Alison E. Hipwell**[5], **Sara S. Nozadi**[6], **Sheela Sathyanarayana**[7,8], **Rosa M. Crum**[9,10], **Rashelle Musci**[10], **Mingyi Li**[9], **Xiuhong Li**[9], **Maxwell Mansolf**[11], **Thomas G. O'Connor**[12], **Amy J. Elliott**[13], **Nidhi Ghildayal**[14], **Pi-I D. Lin**[14], **Jenna L.N. Sprowles**[15], **Joseph B. Stanford**[16], **Casper Bendixsen**[17], **Sally Ozonoff**[18], **Barry M. Lester**[19,20,21], **Coral L. Shuster**[21], **Kathi C. Huddleston**[22], **Jonathan Posner**[23], **Nigel Paneth**[24] **on behalf of program collaborators for Environmental influences on Child Health Outcomes***

[1]Psychology Department, Emory University, Atlanta, GA, USA

[2]Department of Gynecology & Obstetrics, Emory University School of Medicine, Atlanta, GA, USA

[3]Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA

[4]Virginia Commonwealth University School of Nursing, Richmond, VA, USA

[5]Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA

[6]Health Sciences Center University of New Mexico, Albuquerque, NM, USA

[7]Seattle Children's Research Institute, Seattle, WA, USA

[8]University of Washington, Seattle, WA, USA

[9]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[10]Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Corresponding Author Patricia Brennan, Psychology Department, 36 Eagle Row, Emory University, Atlanta, GA 30322, pbren01@emory.edu.

*See Acknowledgments for full listing of collaborators

Contributions

Brennan conceptualized the study and drafted the introduction and discussion, Crum, Musci, Li, Li, and Mansolf completed data coding and analyses and drafted the methods and results sections. All other authors provided data through the ECHO consortium, and provided input on the interpretation of findings, as well as edits to the manuscript.

Conflicts of Interest

None noted

Ethics Approval

Properly constituted Institutional Review Boards – either the ECHO single IRB or the ECHO cohort's local IRB – are accountable for compliance with regulatory requirements for the ECHO-wide Cohort Data Collection Protocol at participating cohort sites. Governing IRBs review ECHO protocols and all informed consent/assent forms, HIPAA authorization forms, recruitment materials, and other relevant information prior to the initiation of any ECHO-wide Cohort Data Collection Protocol-related procedures or activities. ECHO Cohort Investigators (or their designated study personnel) obtain written informed consent or parent's / guardian's permission along with child assent as appropriate, for ECHO-wide Cohort Data Collection Protocol participation and for participation in their specific cohorts. The work of the ECHO Data Analysis Center is approved through the Johns Hopkins Bloomberg School of Public Health Institutional Review Board.

[11]Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

[12]Departments of Psychiatry, Psychology, Neuroscience, and Obstetrics and Gynecology, University of Rochester, Rochester, NY, USA

[13]Avera Research Institute & Dept of Pediatrics, University of South Dakota School of Medicine, Vermillion, SD, USA

[14]Division of Chronic Disease Research Across the Lifecourse, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA

[15]Beckman Institute for Advanced Science and Technology, University of Illinois Urbana-Champaign, Urbana, IL, USA and ICF, Durham, NC

[16]Department of Family and Preventive Medicine and Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT, USA

[17]Marshfield Clinic Research Institute, Marshfield Clinic Health System, Marshfield, WI, USA

[18]Department of Psychiatry and Behavioral Sciences, MIND Institute, University of California Davis, Davis, CA, USA

[19]Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, Providence, RI, USA

[20]Department of Pediatrics, Alpert Medical School of Brown University, Providence, RI, USA

[21]Department of Pediatrics, Women and Infants Hospital of Rhode Island, Providence, RI, USA

[22]College of Health and Human Services, George Mason University, Fairfax, VA, USA

[23]Department of Psychiatry and Behavioral Sciences, Duke University, Durham, NC, USA

[24]Michigan State University, East Lansing, MI, USA

Abstract

Prenatal antidepressant exposure has been associated with increased risk for neurodevelopmental disorders in childhood, including autism spectrum disorder (ASD). The current study utilized multi-cohort data from the Environmental influences on Child Health Outcomes (ECHO) program (*N*=3129) to test for this association, and determine whether the association remained after adjusting for maternal prenatal depression and other potential confounders. Antidepressants and a subset of selective serotonin reuptake inhibitors (SSRIs) were examined in relation to binary (e.g., diagnostic) and continuous measures of ASD and ASD related traits (e.g., social difficulties, behavior problems) in children 1.5 to 12 years of age. Child sex was tested as an effect modifier. While prenatal antidepressant exposure was associated with ASD related traits in univariate analyses, these associations were statistically non-significant in models that adjusted for prenatal maternal depression and other maternal and child characteristics. Sex assigned at birth was not an effect modifier for the prenatal antidepressant and child ASD relationship. Overall, we found no association between prenatal antidepressant exposures and ASD diagnoses or traits. Discontinuation of antidepressants in pregnancy does not appear to be warranted on the basis of increased risk for offspring ASD.

Keywords

antidepressants; prenatal; neurodevelopment; autism spectrum disorder

Approximately 5% to 10% of women in the United States report antidepressant use (primarily selective serotonin reuptake inhibitors [SSRIs]) during pregnancy (Austin, 2006; Huybrechts et al., 2013).Recent studies show SSRI use during pregnancy may be increasing (Bérard et al., 2016; Molenaar et al., 2020). The prevalence of diagnosed autism spectrum disorder (ASD) has also been rising in the United States, leading to a search for environmental exposures that influence risk for this outcome (Chiarotti & Venerosi, 2020). In 2011, a large case-control study exploring the association between prenatal SSRIs and later child neurodevelopmental outcomes linked prenatal SSRI exposure with slightly greater risk for ASD (Croen et al., 2011). This initial report was followed by additional studies and reviews substantiating the link between antidepressant exposures and ASD (Andrade, 2017a; Gentile, 2015; Healy et al., 2016; Kobayashi et al., 2016; Mezzacappa et al., 2017; Rai et al., 2017).

A major concern in the literature on prenatal antidepressant exposure is how to best control for the potentially confounding influence of maternal depression during pregnancy. Prenatal studies often use observational designs that do not control for either prenatal affective disturbance or medication for its treatment. Not all antidepressant exposure studies have incorporated measures of maternal prenatal depression (e.g., Rai et al., 2013). Other studies have inferred maternal prenatal depression status based solely on diagnoses from medical records (e.g., historical diagnoses of Major Depressive Disorder), which may not reflect the actual symptomatology experienced during pregnancy (Brown et al., 2017; Castro et al., 2016; Viktorin et al., 2017). Meta-analyses of the association between maternal antidepressant use during pregnancy and child neurodevelopmental outcomes indicate that confounding by indication is a significant problem in the literature (Andrade, 2017b). Women who are prescribed antidepressants are more likely to have a diagnosis of depression, which in itself carries risk for offspring neurodevelopmental problems. There is a need for studies that measure and control for maternal depression when examining the association between antidepressant medication use in pregnancy and child autism-related outcomes (Rommel et al., 2020).

Considerable heterogeneity of functioning exists among individuals who receive a diagnosis of ASD (Masi et al., 2017). Epidemiological analyses suggest that recent increases in the rates of ASD in the United States are primarily attributed to an increase in mild ASD cases that do not involve intellectual disability (Chiarotti & Venerosi, 2020). Studies that measure social functioning and language deficits have noted poorer performance in these outcome measures for children whose mothers reported antidepressant use in pregnancy (Brandlistuen et al., 2015; Skurtveit et al., 2014; Smearman et al., 2020).

Preclinical studies have also noted changes in social behavior in rodents exposed to SSRIs during the perinatal period, providing experimental evidence for causal associations between social behavior and SSRIs (Gemmel et al., 2018; Houwing et al., 2019). Studies also suggest that biological sex might act as an effect modifier of prenatal SSRI exposure,

with poorer neurodevelopmental outcomes typically noted in males relative to females (Leussis et al., 2021). The aims of the current study are to examine associations between prenatal antidepressant exposures and child ASD diagnoses and traits, to test whether these associations are stronger for male offspring relative to female offspring, and to assess whether any noted prenatal medication and ASD associations remain significant when maternal depression and other relevant confounds are controlled.

The current study examines data from the Environmental influences on Child Health Outcomes (ECHO) program, which combines longitudinal data across ongoing child cohort studies throughout the United States (Gillman & Blaisdell, 2018). Use of the ECHO-wide data set allows for a diverse and nationally representative sample, in contrast to the majority of previous studies where samples were limited to one geographic area within the country (Molenaar et al., 2020). We completed secondary analyses of data from 22 unique cohorts (including community cohorts, and case-control cohorts) in the ECHO-wide consortium to test the following hypotheses: (1) Prenatal exposure to any antidepressant medication, and to the subset of SSRI medications in particular, will be associated with a childhood ASD diagnosis and autism-related traits. (2) These hypothesized associations will persist when controlling for potentially confounding maternal and child characteristics, including prenatal maternal depression. (3) Child sex will act as an effect modifier in the association between prenatal antidepressant exposure and child ASD-related outcomes, with males being more susceptible to the exposure than females.

Methods

Participants

This study included mother-child dyads from the ECHO-wide Cohort with available data on prenatal exposure to antidepressants as well as measures of ASD and/or autism-related traits collected when the child was between 1 and 12 years of age (N=3129). Table 1 shows demographic and prenatal characteristics of women in the sample who took antidepressants during pregnancy (approximately 5% of the sample) compared with those who did not take antidepressants during pregnancy.

Measures

The current study utilized ECHO prenatal exposure and child neurodevelopmental measures as detailed below. Data were collected according to the ECHO data collection protocol (https://echochildren.org/wp-content/uploads/2021/05/ECHO-wide-Cohort-Data-Collection-Protocol-Version2.0_24FEB2021_clean.pdf).

Maternal Prenatal Antidepressant and SSRI Use—Information on maternal prenatal antidepressant medication use was obtained from two sources in the ECHO database: the *Maternal Medical Record Abstraction* form (MMRA), and the *Pregnancy Medical Conditions and Interventions* (PMCI) questionnaire completed by the mothers. The MMRA was completed once for each pregnancy included in ECHO. Information was gathered for the period from 4 weeks prior to the last menstrual period (LMP) before the pregnancy through 8 weeks postpartum. All medications listed in the medical records were recorded

with notation of timing before, during, or after pregnancy. The PMCI was completed by the biological mother for each pregnancy resulting in a child (or children) being enrolled in an ECHO cohort. The questionnaire, completed during the child's infancy, early childhood, or middle childhood life stages, asked about the mother's health, medical conditions she had before or during pregnancy, tests or procedures that were done, and medical complications that occurred during pregnancy, labor, and/or delivery. Mothers also reported whether they had taken medication for depression during their pregnancy. A detailed list of antidepressants was provided that included generic and brand names as well as options for adding additional medications that were not specified. The most common type of antidepressant medications used by mothers in this study was SSRIs (~72%), and the most common SSRI medications were paroxetine and sertraline.

Binary Measures of ASD—ASD diagnosis was obtained from several sources including established standardized diagnostic instruments, such as the *Autism Diagnostic Observation Schedule* (ADOS; Lord et al., 2000), parental or other caregiver report of an ASD diagnosis, or a diagnosis extracted from medical or educational records. A subset of mothers also completed the *Modified Checklist for Autism in Toddlers-Revised with Follow-up* (M-CHAT-R/F; Robins et al., 2014). This 20-item checklist has demonstrated reliability and validity as a screener for ASD in typically developing toddlers (ages 16 to 30 months old). Children were categorized as above and below the cut-off for probable ASD according to their score on the M-CHAT-R/F. These bivariate measures of ASD (i.e., diagnoses and M-CHAT-R/F screener results) were examined as separate outcomes in this study.

Continuous Measures of Child Autism-Related Traits—Mothers completed the *Social Responsiveness Scale, Second Edition* (SRS-2; Constantino & Gruber, 2012) about their child. The SRS-2 is a 65-item scale that evaluates the severity of ASD symptoms occurring in day-to-day scenarios. The preschool version was used for children aged 31 months through 47 months, and the school-age version was used for children from ages 4 to 12 years. The overall raw score was used—higher scores reflect more autism-related traits. Mothers also completed the *Preschool-Age Child Behavior Checklist* (preschool CBCL; Achenbach & Rescorla, 2000) in reference to their children aged 18 months to five years of age. The *DSM-5 Autism Spectrum Problems* (ASP) subscale of the preschool CBCL assesses the occurrence of 12 child behaviors over the previous 2 months that were rated by international clinical experts as "very consistent" with ASD, such as avoiding eye contact and not getting along with others (Achenbach, 2014). Higher scores indicate more ASD-related behaviors. Mothers also completed the *School-Age Child Behavior Checklist* (school-age CBCL; Achenbach, 2001) in reference to their children aged 6 to 12 years of age. *t*-scores on the Withdrawn, Social Problems, and Thought Problems subscales were summed to create a school-age CBCL ASD-related behavior score for each child. This score has been shown to discriminate between children with and without ASD, particularly among high-functioning youth (Biederman et al., 2010).

Covariates—We used a directed acyclic graph (see Supplemental Figure 1) to decide what covariates to include in analyses based on conceptual and empirical justification from the existing literature. Maternal prenatal depression was included as a covariate and

was considered present if the maternal medical record indicated this as a condition, or if the mother self-reported this condition on the PMCI questionnaire. Additional covariates included the following maternal characteristics: age, education, race/ethnicity (non-Hispanic White versus others), marital status, prenatal substance use (tobacco, alcohol, marijuana), and pre-pregnancy BMI (obtained from medical record abstractions); as well as the child characteristics of age and sex.

Statistical Analysis

Observations in this study conformed to assumptions of independence. In cases of multiple sibling participation, one sibling was randomly selected for inclusion in the study. In cases of multiple administrations of the same maternal reported measure of ASD, the measure completed at the youngest child age (closest to the prenatal exposure) was selected for inclusion in the analyses. General antidepressant use and SSRI use were examined in separate analyses, as were ASD and autism-related traits. Medical record and self-report indicators of prenatal exposure to antidepressants were examined separately (in univariate models) and combined (in univariate and multivariate models). Multiple imputation chained equations models (van Buuren & Groothuis-Oudshoorn, 2011) were used to account for the missingness in covariates, including child's age at visit for each outcome variable, child's sex, prenatal depression diagnosis, maternal age, maternal race/ethnicity (non-Hispanic White versus others), maternal education level, maternal marital status, prenatal tobacco use, prenatal alcohol use, prenatal marijuana use, and pre-pregnancy BMI. Regression estimates were pooled based on the combination of 25 imputations using the Rubin's rules (Rubin, 2004). Data were not imputed for prenatal medications or ASD outcomes, so analyses had varying sample sizes (as reported in the results tables).

Mixed-effects models were used to perform univariate and multivariate analyses, adjusting for cohort effects by including cohort as a random intercept in the models. Linear mixed-effects models were used for continuous outcomes (using the "lmer" function from the "lme4" R package), examining coefficients, confidence intervals (CIs), and *P*-values from these models. Mixed-effects logistic models were used for binary outcomes (using the "glmer" function from the "lme4" R package), examining odds ratios, CIs, and *P*-values. Models were fitted with maximum likelihood estimators. Wald 95% CIs were constructed, and *P*-values were derived from the Wald z-test.

Univariate analyses examined prenatal antidepressant and SSRI exposure as the predictor and child ASD measures as the outcome. The interaction term of child sex and each prenatal antidepressant and SSRI exposure was tested to assess whether sex was a significant effect modifier. Finally, multivariate analyses were performed by including all covariates in the model and assessing for independent effects of prenatal antidepressant or SSRI exposures on each ASD outcome. All analyses were conducted in R software version 4.1.0.

Results

Our hypothesis that prenatal exposures to antidepressants (and the subset of SSRI medications) would be associated with child ASD and autism-related traits was partially supported in univariate analyses. As can be seen in Table 2, neither SSRI use nor general

antidepressant use in pregnancy was associated with ASD diagnoses or with M-CHAT-R/F cut-off scores. However, analyses that included continuous measures of ASD-related traits revealed that any prenatal antidepressant use (and self-reported antidepressant use in particular) predicted higher child SRS-2 total raw scores. In addition, prenatal SSRI use (and self-reported SSRI use in particular) predicted higher child preschool CBCL-ASP *t*-scores, and self-reported prenatal antidepressant use was significantly associated with higher child school-age CBCL sum *t*-scores for ASD.

Child sex was also explored as an effect modifier of the association between prenatal antidepressant/SSRI exposure and child ASD outcomes. No exposure-child sex interaction terms were statistically significant. Table 3 presents the univariate associations separated by sex.

Multivariate regression analyses did not support our second hypothesis that prenatal medication and child ASD outcome relationships would hold when controlling for child age, child sex, maternal age, maternal race/ethnicity, maternal marital status, maternal education, prenatal substance exposures, pre-pregnancy BMI, and prenatal maternal depression (see Tables 4 and 5). Neither prenatal antidepressant use nor SSRI use predicted any of the ASD outcome measures when these potential confounders were controlled.

To check whether missingness on our maternal prenatal depression variable was related to ASD outcomes, univariable mixed logistic regression models (adjusting for the cohort effect) were performed, including maternal prenatal depression as a dependent variable and each ASD outcome as a predictor. Results showed that missingness on maternal prenatal depression was unrelated to all ASD outcomes with the exception of ASD diagnoses. Cases with missing data for prenatal depression, compared to those without missing data, had significantly higher odds of receiving ASD diagnoses (p=.0032). Since ASD outcomes were included in the imputation models, this difference should be addressed through our statistical procedures.

Sensitivity analyses were performed to test whether imputation strategies, cohort study design (case control for ASD versus community cohort), self-report versus medical record source of prenatal medication data, or timing of maternal self-report prenatal medication use substantially impacted study findings. Results from sensitivity analyses confirmed the primary findings in all cases (see supplementary tables).

Discussion

The current study expands upon the previous literature by utilizing data from the ECHO-wide Cohort, a national cohort of mother-child pairs, to examine the association between prenatal antidepressant/SSRI exposures and both binary (diagnostic) and continuous (behavior and symptom scales) ASD-related outcomes.

One of the methodological constraints in observational studies of prenatal antidepressant exposures and child health outcomes is confounding by indication. Specifically, women who are prescribed and/or continue the use of antidepressants in pregnancy are more likely to suffer from more severe depression. These women may also systematically

differ from others in terms of demographic or other health characteristics that might confound the association between prenatal antidepressant exposures and child ASD-related behaviors. In the current study, statistical control for these potential confounds rendered initial univariate associations between prenatal exposure and child ASD-related behavior associations statistically non-significant. Our study adds to the growing consensus in the field that prenatal antidepressant exposure is not causally associated with ASD, as evidenced by results from well-controlled observational studies, as well as sibling control designs that account for maternal depression and/or genetic risk (Ames et al., 2021; Vega et al., 2020).

The current study examined ASD outcomes as measured by both bivariate/diagnostic indicators and continuous measures of ASD traits. Importantly, the continuous maternal report measures capture behaviors that are often associated with ASD but are not necessarily unique to the disorder. Recent studies have found associations between prenatal antidepressant exposure and child neurodevelopmental problems outside of the realm of ASD, including affective disorders (Rommel et al., 2020), attention deficit hyperactivity disorder (Clements et al., 2015), and pragmatic language deficits (Smearman et al., 2020). It is possible that symptomatology overlap between ASD and other neurodevelopmental disorders has led to noted associations between prenatal antidepressant exposures and ASD outcomes in previous research.

We found that maternal race was associated with antidepressant use during pregnancy in the ECHO cohort, with medication rates being higher for White participants. This finding is consistent with survey reports of racial disparities in mental health treatment for pregnant women in the U.S. (Salameh et al., 2019), and it may also reflect racial differences in preference for treatment with pharmacotherapy in the perinatal period (Goodman et al., 2013). The significant associations noted between marital status and ASD-related outcomes are consistent with previous studies demonstrating higher divorce rates in families with children with ASD (Hartley et al, 2010), and likely reflect the financial and emotional stressors associated with raising a child with a disability (Karst & Van Hecke, 2012).

We examined whether child biological sex was an effect modifier in the association between prenatal antidepressant exposure and child ASD-related outcomes. Contrary to what has been seen in some preclinical (Leussis et al., 2021) and human (Harrington et al., 2014) studies, and contrary to our hypothesis, biological sex did not interact with prenatal antidepressant or SSRI exposures to predict ASD-related outcomes in this multi-cohort analysis. It is possible that other untested risk or protective factors might significantly influence the prenatal medication exposure and child neurodevelopmental outcome associations. As larger cohort studies and meta-analyses are becoming more common in this research area, tests of other potential effect modifiers might be useful to inform clinical decision-making strategies (e.g., discontinuation of antidepressant use) for obstetricians and pregnant women in their care.

The results of our study were relatively consistent for any antidepressant use versus the subset of SSRIs. We did not have sufficient power to assess the potential impact of specific medications or the timing of exposures during pregnancy. More fine-grained analyses of these indicators would be informative for both theoretical and clinical purposes.

If deleterious impacts of prenatal antidepressant use are medication-specific or trimester-specific, analyses that combine all antidepressant use in pregnancy into a single predictor may mask these differences.

When left untreated, maternal prenatal depression has been associated with a number of adverse child outcomes including birth complications and higher rates of psychopathology (Barker et al., 2011). Treatment decisions for pregnant women are multifaceted and require weighing a number of differential risks. Findings from the current study of a large, multi-cohort population suggest that prenatal antidepressant exposure does not increase the risk for ASD and autism-related traits, once maternal prenatal depression and other demographic confounders are controlled. These results suggest that the discontinuation of antidepressant use in pregnancy to decrease risk for ASD may not be warranted, particularly if it is not clinically indicated by maternal depression status or history.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Descriptive characteristics of mothers with and without antidepressant use during pregnancy in the ECHO wide cohort

	Mothers without any antidepressant use (N=2966)	Mothers with any antidepressant use (N=163)	P-value
Depression diagnosis? during pregnancy			
No	1771 (59.7%)	13 (8.0%)	<0.001
Yes	170 (5.7%)	88 (54.0%)	
Missing	1025 (34.6%)	62 (38.0%)	
Age at the birth of the first child			
Mean (SD)	30.7 (5.51)	31.3 (5.23)	0.172
Median [Min, Max]	31.0 [15.0, 50.0]	31.0 [16.0, 45.0]	
Missing	18 (0.6%)	0 (0%)	
Race category			
White	2093 (70.6%)	133 (81.6%)	<0.001
Black	282 (9.5%)	<5 (<3.1%)	
Asian	135 (4.6%)	0 (0%)	
American Indian or Alaska Native	16 (0.5%)	0 (0%)	
Multiple Race	34 (1.1%)	0 (0%)	
Native Hawaiian or other Pacific Islander	162 (5.5%)	8 (4.9%)	
Other Race	88 (3.0%)	0 (0%)	
Missing	156 (5.3%)	<20 (<12.3%)	
Ethnicity			
non-Hispanic	2485 (83.8%)	134 (82.2%)	0.307
Hispanic	360 (12.1%)	14 (8.6%)	
Missing	121 (4.1%)	15 (9.2%)	
Highest education [a]			
Less than high school	104 (3.5%)	<5 (<3.1%)	0.225
High school degree	292 (9.8%)	10 (6.1%)	
Some college without degree	792 (26.7%)	49 (30.1%)	
Bachelor’s degree	903 (30.4%)	50 (30.7%)	
Master’s degree or above	836 (28.2%)	51 (31.3%)	
Missing	39 (1.3%)	<5 (<3.1%)	
Marital status [b]			
Married	2438 (82.2%)	133 (81.6%)	0.375
Not married	445 (15.0%)	<30 (< 18.4%)	
Missing	83 (2.8%)	<5 (<3.1%)	
Income of the household, 5 categories			
<$30,000	354 (11.9%)	17 (10.4%)	0.938
$30,000–$49,999	227 (7.7%)	13 (8.0%)	
$50,000–$74,999	238 (8.0%)	14 (8.6%)	

	Mothers without any antidepressant use (N=2966)	Mothers with any antidepressant use (N=163)	P-value
$75,000–$99,999	153 (5.2%)	10 (6.1%)	
$100,000 or more	317 (10.7%)	17 (10.4%)	
Missing	1677 (56.5%)	92 (56.4%)	
Mode of delivery for the first child			
vaginal	1763 (59.4%)	83 (50.9%)	0.64
cesarean	935 (31.5%)	48 (29.4%)	
Missing	268 (9.0%)	32 (19.6%)	
Gestational age at birth			
Mean (SD)	35.7 (5.56)	37.0 (4.31)	<0.001
Median [Min, Max]	38.0 [22.0, 43.0]	39.0 [23.0, 42.0]	
Missing	11 (0.4%)	0 (0%)	
Prenatal tobacco/nicotine use			
No	2612 (88.1%)	130 (79.8%)	0.045
Yes	264 (8.9%)	22.0 (13.5%)	
Missing	90.0 (3.0%)	11.0 (6.7%)	
Prenatal alcohol use			
No	2373 (80.0%)	125 (76.7%)	0.206
Yes	421 (14.2%)	29 (17.8%)	
Missing	172 (5.8%)	9 (5.5%)	
Prenatal illicit drug use			
No	2305 (77.7%)	119 (73.0%)	0.683
Yes	32 (1.1%)	<5 (3.1%)	
Missing	629 (21.2%)	<45 (27.6%)	
Prenatal marijuana use			
No	2386 (80.4%)	122 (74.8%)	0.816
Yes	99 (3.3%)	<5 (<3.1%)	
Missing	481 (16.2%)	<40 (<24.5%)	
Pre-pregnancy BMI, kg/m^2			
Mean (SD)	27.1 (6.99)	29.8 (8.30)	<0.001
Median [Min, Max]	25.2 [15.6, 73.1]	28.1 [15.8, 60.9]	
Missing	401 (13.5%)	26 (16.0%)	

a. Some college without degree also includes associate degree and trade school. Master's degree or above also includes (professional) doctoral degrees.

b. Married stands for Married or living with a partner; Not married includes widowed, separated, divorced, single, never married, and partnered (boyfriend or girlfriend) but not living together.

c. preterm gestational category is defined as gestational age at birth from 22 to 36 weeks.

d. P-values were given from the t-test for continuous variables or chi-square test for categorical variables.

Table 2.

Estimated univariate associations between ASD related outcomes and prenatal antidepressant and SSRI use

Associations (exposed vs. unexposed groups for outcomes)	N-Total	N-Exposed	Coefficient/OR	LCL	UCL	P-value
SRS total raw score, N=1346						
Any antidepressant	1339	76	6.4	1.0	11.9	0.02
SSRI	1214	50	6.5	−0.3	13.3	0.06
Medical reported any antidepressant	118	8	11.4	−12.0	34.9	0.34
Medical reported SSRI	120	7	14.3	−11.4	39.9	0.28
Self-reported any antidepressant	1221	68	5.7	0.2	11.2	0.04
Self-reported SSRI	1094	43	5.1	−1.7	12.0	0.14
CBCL DSM-5 Autism t score for preschool children, N=1202						
Any antidepressant	1199	63	1.0	−0.7	2.6	0.25
SSRI	1072	38	2.2	0.1	4.4	0.04
Medical reported any antidepressant	59	6	1.1	−3.7	6.0	0.65
Medical reported SSRI	58	5	2.0	−3.3	7.2	0.47
Self-reported any antidepressant	1140	57	1.0	−0.7	2.7	0.25
Self-reported SSRI	1014	33	2.4	0.1	4.7	0.04
CBCL Autism Sum t score for school age children, N=546						
Any antidepressant	546	35	5.0	−0.3	10.3	0.07
SSRI	477	22	0.9	−5.7	7.6	0.78
Medical reported any antidepressant	59	<5	NA	NA	NA	NA
Medical reported SSRI	59	<5	NA	NA	NA	NA
Self-reported any antidepressant	487	32	5.5	0.4	10.6	0.03
Self-reported SSRI	418	19	1.2	−5.3	7.7	0.73
ASD diagnosis, N=2384						
Any antidepressant	2377	98	1.3	0.6	2.7	0.51
SSRI	2323	76	1.8	0.7	4.2	0.20
Medical reported any antidepressant	515	21	1.2	0.4	3.4	0.76
Medical reported SSRI	512	15	1.9	0.5	7.1	0.32
Self-reported any antidepressant	1862	77	1.4	0.5	4.1	0.49
Self-reported SSRI	1811	61	1.7	0.5	5.6	0.40
M-CHAT, N=834						
Any antidepressant	831	41	1.3	0.4	4.0	0.64
SSRI	761	23	1.0	0.2	4.5	0.98
Medical reported any antidepressant	42	<5	NA	NA	NA	NA
Medical reported SSRI	42	<5	NA	NA	NA	NA
Self-reported any antidepressant	789	37	1.7	0.5	5.5	0.35
Self-reported SSRI	719	19	1.5	0.3	7.6	0.60

[a]N, number of subjects; LCL, lower confidence limit; UCL, upper confidence limit; OR, odds ratio.

[b] SRS total raw score, CBCL DSM-5 Autism t score, CBCL Autism Sum t score are continuous outcomes. The estimated coefficient of exposure are given in the third column. ASD diagnosis and M-CHAT are binary outcomes. The estimated OR for each binary outcome variable comparing the exposed and unexposed groups are given in the third column.

[c] NA, not applicable. It represents that corresponding model did not converge or the estimations were too extreme to be true.

Table 3.

Estimated univariate associations between ASD-related outcomes and prenatal antidepressant use, using child's sex as the effect modification

Associations (exposed vs. unexposed groups for outcomes)	Child's sex	N	Coefficient/OR	LCL	UCL	*P*-value
SRS-2 total raw score, N=1346						
Any antidepressant	Male	732	6.8	−1.4	15.0	0.12
	Female	607	5.8	−3.5	15.1	0.30
	Interaction		−1	−11.8	9.8	0.12
SSRI	Male	664	7.2	−2.6	17.0	0.19
	Female	550	4.5	−7.9	16.9	0.66
	Interaction		−2.7	−16.5	11.1	0.19
Medical reported any antidepressant	Male	70	15.6	−17.8	49.0	0.51
	Female	48	5.0	−38.4	48.4	0.96
	Interaction		−10.6	−58.3	37	0.5
Medical reported SSRI	Male	71	20.5	−18.1	59.0	0.42
	Female	49	5.6	−39.1	50.3	0.95
	Interaction		−14.9	−66.6	36.8	0.41
Self-reported any antidepressant	Male	662	5.6	−2.7	13.8	0.25
	Female	559	5.7	−3.6	15.0	0.31
	Interaction		0.1	−10.7	11	0.25
Self-reported SSRI	Male	593	5.3	−4.5	15.2	0.40
	Female	501	3.5	−9.2	16.3	0.78
	Interaction		−1.8	−15.9	12.3	0.4
CBCL DSM-5 ASP *t*-score for preschool children, N=1202						
Any antidepressant	Male	653	1.1	−1.2	3.5	0.49
	Female	546	0.5	−2.4	3.5	0.90
	Interaction		−0.6	−3.9	2.7	0.49
SSRI	Male	577	2.5	−0.5	5.6	0.13
	Female	495	1.4	−2.5	5.4	0.66
	Interaction		−1.1	−5.5	3.3	0.13
Medical reported any antidepressant	Male	33	−2.9	−12.2	6.3	0.73
	Female	26	3.5	−3.4	10.4	0.45
	Interaction		6.4	−3.7	16.5	0.73
Medical reported SSRI	Male	32	−2.4	−15.4	10.6	0.90
	Female	26	3.5	−3.4	10.4	0.45
	Interaction		5.9	−7	18.8	0.9
Self-reported any antidepressant	Male	620	1.4	−1.1	3.8	0.39
	Female	520	0.2	−3.0	3.3	0.99
	Interaction		−1.2	−4.7	2.3	0.39
Self-reported SSRI	Male	545	2.7	−0.4	5.9	0.10

Associations (exposed vs. unexposed groups for outcomes)	Child's sex	N	Coefficient/OR	LCL	UCL	*P*-value
	Female	469	1.0	−3.7	5.7	0.86
	Interaction		−1.7	−6.7	3.2	0.1
CBCL autism sum *t*-score for school-age children, N=546						
Any antidepressant	Male	301	5.6	−2.6	13.8	0.23
	Female	245	4.2	−4.7	13.1	0.50
	Interaction		−1.4	−12	9.2	0.23
SSRI	Male	268	1.4	−8.5	11.3	0.94
	Female	209	0.1	−11.8	12.0	1.00
	Interaction		−1.3	−14.9	12.3	0.94
Medical reported any antidepressant	Male	44	NA	NA	NA	NA
	Female	15	NA	NA	NA	NA
	Interaction		NA	NA	NA	NA
Medical reported SSRI	Male	44	NA	NA	NA	NA
	Female	15	NA	NA	NA	NA
	Interaction		NA	NA	NA	NA
Self-reported any antidepressant	Male	257	6.5	−1.5	14.6	0.14
	Female	230	4.7	−3.4	12.8	0.35
	Interaction		−1.9	−11.9	8.2	0.14
Self-reported SSRI	Male	224	1.9	−8.2	12.1	0.89
	Female	194	0.4	−10.3	11.1	1.00
	Interaction		−1.6	−14.5	11.3	0.89
ASD diagnosis, N=2384						
Any antidepressant	Male	1304	1.1	0.4	3.0	0.94
	Female	1073	1.5	0.3	8.8	0.85
	Interaction		1.3	0.2	7.7	0.94
SSRI	Male	1274	2.2	0.7	6.7	0.24
	Female	1049	0.8	0.1	9.2	0.97
	Interaction		0.4	0.03	3.9	0.24
Medical reported any antidepressant	Male	325	1.1	0.3	4.2	0.98
	Female	190	1.3	0.1	22.9	0.98
	Interaction		1.2	0.1	18.9	0.98
Medical reported SSRI	Male	321	2.4	0.4	14.7	0.51
	Female	191	1.3	0.1	23.0	0.98
	Interaction		0.5	0.03	10.9	0.51
Self-reported any antidepressant	Male	979	1.2	0.3	5.0	0.93
	Female	883	1.7	0.2	17.3	0.84
	Interaction		1.4	0.1	14.7	0.93
Self-reported SSRI	Male	953	NA	NA	NA	NA
	Female	858	NA	NA	NA	NA

Associations (exposed vs. unexposed groups for outcomes)	Child's sex	N	Coefficient/OR	LCL	UCL	*P*-value
	Interaction		NA	NA	NA	NA
M-CHAT-R/F, N=834						
Any antidepressant	Male	451	1.5	0.3	6.7	0.80
	Female	380	0.9	0.1	10.0	1.00
	Interaction		0.6	0.1	7.2	0.8
SSRI	Male	412	NA	NA	NA	NA
	Female	349	NA	NA	NA	NA
	Interaction		NA	NA	NA	NA
Medical reported any antidepressant	Male	22	NA	NA	NA	NA
	Female	20	NA	NA	NA	NA
	Interaction		NA	NA	NA	NA
Medical reported SSRI	Male	22	NA	NA	NA	NA
	Female	20	NA	NA	NA	NA
	Interaction		NA	NA	NA	NA
Self-reported any antidepressant	Male	429	1.8	0.4	8.3	0.65
	Female	360	1.4	0.1	15.8	0.94
	Interaction		0.8	0.1	9.3	0.65
Self-reported SSRI	Male	390	NA	NA	NA	NA
	Female	329	NA	NA	NA	NA
	Interaction		NA	NA	NA	NA

ASD, autism spectrum disorder; *CBCL*, Child Behavior Checklist; *LCL*, lower confidence limit; *M-CHAT-R/F*, Modified Checklist for Autism in Toddlers-Revised with Follow-up; *NA*, not applicable; *OR*, odds ratio; *SRS-2*, Social Responsiveness Scale, Second Edition; *SSRI*, selective serotonin reuptake inhibitors; *UCL*, upper confidence limit

SRS-2 total raw score, CBCL DSM-5 Autism *t*-score, and CBCL autism sum *t*-score are continuous outcomes. The estimated coefficients of exposure are given in the third column. ASD diagnosis and M-CHAT-R/F are binary outcomes. The estimated OR for each binary outcome variable comparing the exposed and unexposed groups are given in the third column. NA represents that the corresponding model did not converge or the estimations were too extreme to be true.

Table 4.

Estimated adjusted associations between ASD related outcomes and prenatal antidepressant use exposure

Models	Coefficient/OR	LCL	UCL	P-value
SRS total raw ~ any antidepressant, N=1339				
Any prenatal antidepressant use: Yes vs. No	2.5	−4.1	9.1	0.45
Age at visit for the outcome, yrs	0.5	−0.2	1.3	0.17
Child's sex: Female vs. Male	−4.3	−6.7	−1.9	0.001
Prenatal depression diagnosis: Yes vs. No	2.9	−1.9	7.7	0.24
Maternal age at delivery, yrs	0.0	−0.2	0.2	0.98
Maternal Non-Hispanic white vs. others	−3.1	−5.9	−0.2	0.03
Maternal above vs. less than high school education	−9.6	−13.5	−5.6	<0.001
Maternal not married vs. married	8.7	5.1	12.3	<0.001
Prenatal tobacco use: Yes vs. No	4.1	−0.6	8.7	0.09
Prenatal alcohol use: Yes vs. No	0.3	−3.4	4.1	0.86
Prenatal marijuana use: Yes vs. No	1.2	−5.9	8.4	0.74
Pre-pregnancy BMI, kg/m^2	0.3	0.2	0.5	<0.001
CBCL DSM-5 Autism t score for preschool children ~ any antidepressant, N=1199				
Any prenatal antidepressant use: Yes vs. No	−0.4	−2.4	1.6	0.69
Age at visit for the outcome, yrs	0.0	−0.5	0.5	0.89
Child's sex: Female vs. Male	−0.9	−1.6	−0.2	0.02
Prenatal depression diagnosis: Yes vs. No	1.6	0.0	3.1	0.05
Maternal age at delivery, yrs	0.0	−0.1	0.1	0.90
Maternal Non-Hispanic white vs. others	−0.7	−1.5	0.1	0.11
Maternal above vs. less than high school education	−1.2	−2.3	−0.2	0.02
Maternal not married vs. married	1.6	0.5	2.6	0.003
Prenatal tobacco use: Yes vs. No	0.7	−0.5	2.0	0.26
Prenatal alcohol use: Yes vs. No	−1.1	−2.2	−0.1	0.04
Prenatal marijuana use: Yes vs. No	1.0	−0.7	2.6	0.24
Pre-pregnancy BMI, kg/m^2	0.0	0.0	0.1	0.16
CBCL Autism Sum t score for school age children~ any antidepressant, N=546				
Any prenatal antidepressant use: Yes vs. No	5.0	−2.0	12.0	0.16
Age at visit for the outcome, yrs	−0.1	−1.5	1.3	0.89
Child's sex: Female vs. Male	−3.2	−5.8	−0.7	0.01
Prenatal depression diagnosis: Yes vs. No	−1.4	−7.1	4.3	0.64
Maternal age at delivery, yrs	−0.1	−0.3	0.1	0.42
Maternal Non-Hispanic white vs. others	−0.5	−3.6	2.7	0.76
Maternal above vs. less than high school education	−0.5	−5.6	4.7	0.86
Maternal not married vs. married	7.1	2.8	11.4	0.001
Prenatal tobacco use: Yes vs. No	2.1	−2.5	6.8	0.37

Models	Coefficient/OR	LCL	UCL	P-value
Prenatal alcohol use: Yes vs. No	3.6	−0.3	7.5	0.07
Prenatal marijuana use: Yes vs. No	12.1	0.1	24.1	0.05
Pre-pregnancy BMI, kg/m^2	0.4	0.2	0.7	<0.001
ASD diagnosis~ any antidepressant, N=2377				
Any prenatal antidepressant use: Yes vs. No	1.0	0.4	2.3	0.97
Age at visit for the outcome, yrs	1.2	1.1	1.4	0.01
Child's sex: Female vs. Male	0.4	0.3	0.6	<0.001
Prenatal depression diagnosis: Yes vs. No	1.3	0.8	2.2	0.26
Maternal age at delivery, yrs	1.0	1.0	1.0	0.32
Maternal Non-Hispanic white vs. others	1.2	0.9	1.7	0.29
Maternal above vs. less than high school education	0.9	0.6	1.4	0.66
Maternal not married vs. married	1.3	0.8	1.9	0.25
Prenatal tobacco use: Yes vs. No	1.4	0.9	2.2	0.19
Prenatal alcohol use: Yes vs. No	0.6	0.3	1.2	0.17
Prenatal marijuana use: Yes vs. No	0.8	0.4	1.7	0.63
Pre-pregnancy BMI, kg/m^2	1.0	1.0	1.0	0.48
MCHAT~ any antidepressant, N=831				
Any prenatal antidepressant use: Yes vs. No	1.4	0.3	5.6	0.64
Age at visit for the outcome, yrs	0.8	0.5	1.3	0.34
Child's sex: Female vs. Male	0.5	0.4	0.8	0.01
Prenatal depression diagnosis: Yes vs. No	0.8	0.3	2.1	0.67
Maternal age at delivery, yrs	1.02	0.99	1.1	0.23
Maternal Non-Hispanic white vs. others	1.0	0.6	1.5	0.88
Maternal above vs. less than high school education	0.4	0.2	0.6	<0.00
Maternal not married vs. married	1.9	1.1	3.1	0.01
Prenatal tobacco use: Yes vs. No	1.7	0.9	3.1	0.09
Prenatal alcohol use: Yes vs. No	1.0	0.4	3.0	0.94
Prenatal marijuana use: Yes vs. No	0.7	0.3	1.5	0.32
Pre-pregnancy BMI, kg/m^2	1.01	0.99	1.04	0.32

ASD, autism spectrum disorder; *BMI*, body mass index; *CBCL*, Child Behavior Checklist; *LCL*, lower confidence limit; *M-CHAT-R/F*, Modified Checklist for Autism in Toddlers-Revised with Follow-up; *OR*, odds ratio; *SRS-2*, Social Responsiveness Scale, Second Edition; *UCL*, upper confidence limit

Table 5.

Estimated adjusted associations between ASD related outcomes and prenatal SSRI use exposure

Models	Coefficient/OR	LCL	UCL	P-value
SRS total raw ~ SSRI, N=1214				
Prenatal SSRI use Yes vs. No	0.9	−6.8	8.6	0.82
Age at visit for the outcome, yrs	0.4	−0.5	1.2	0.39
Child's sex: Female vs. Male	−4.4	−7.0	−1.8	0.001
Prenatal depression diagnosis: Yes vs. No	4.2	−0.8	9.2	0.10
Maternal age at delivery, yrs	0.0	−0.2	0.3	0.87
Maternal Non-Hispanic white vs. others	−3.0	−6.1	0.1	0.06
Maternal above vs. less than high school education	−10.2	−14.4	−6.0	<0.001
Maternal not married vs. married	8.6	4.7	12.4	<0.001
Prenatal tobacco use: Yes vs. No	2.5	−2.2	7.3	0.30
Prenatal alcohol use: Yes vs. No	0.2	−3.9	4.2	0.94
Prenatal marijuana use: Yes vs. No	2.2	−5.4	9.7	0.57
Pre-pregnancy BMI, kg/m^2	0.4	0.2	0.6	<0.001
CBCL DSM-5 Autism t score for preschool children ~ SSRI, N=1072				
Prenatal SSRI use Yes vs. No	0.4	−2.1	2.9	0.76
Age at visit for the outcome, yrs	0.01	−0.6	0.6	0.98
Child's sex: Female vs. Male	−0.8	−1.6	−0.1	0.04
Prenatal depression diagnosis: Yes vs. No	1.9	0.2	3.5	0.03
Maternal age at delivery, yrs	−0.02	−0.1	0.1	0.70
Maternal Non-Hispanic white vs. others	−0.7	−1.6	0.2	0.13
Maternal above vs. less than high school education	−1.2	−2.3	−0.1	0.04
Maternal not married vs. married	1.5	0.3	2.6	0.01
Prenatal tobacco use: Yes vs. No	0.7	−0.6	2.0	0.29
Prenatal alcohol use: Yes vs. No	−1.2	−2.4	−0.1	0.04
Prenatal marijuana use: Yes vs. No	1.2	−0.6	2.9	0.20
Pre-pregnancy BMI, kg/m^2	0.04	−0.01	0.1	0.15
CBCL Autism Sum t score for school age children ~ SSRI, N=477				
Prenatal SSRI use Yes vs. No	1.1	−6.8	9.0	0.79
Age at visit for the outcome, yrs	−0.6	−2.2	1.0	0.48
Child's sex: Female vs. Male	−3.0	−5.8	−0.2	0.04
Prenatal depression diagnosis: Yes vs. No	−2.7	−8.4	3.0	0.35
Maternal age at delivery, yrs	−0.1	−0.3	0.2	0.50
Maternal Non-Hispanic white vs. others	0.5	−3.0	4.1	0.77
Maternal above vs. less than high school education	−1.0	−6.6	4.5	0.71
Maternal not married vs. married	6.9	2.3	11.5	0.003
Prenatal tobacco use: Yes vs. No	1.9	−2.9	6.7	0.44

Models	Coefficient/OR	LCL	UCL	P-value
Prenatal alcohol use: Yes vs. No	3.6	−0.6	7.9	0.09
Prenatal marijuana use: Yes vs. No	16.1	2.9	29.3	0.02
Pre-pregnancy BMI, kg/m^2	0.5	0.3	0.7	<0.001
ASD diagnosis ~ SSRI, N=2323				
Prenatal SSRI use Yes vs. No	1.5	0.6	3.5	0.38
Age at visit for the outcome, yrs	1.2	1.1	1.4	0.004
Child's sex: Female vs. Male	0.4	0.3	0.6	<0.001
Prenatal depression diagnosis: Yes vs. No	1.2	0.8	1.8	0.49
Maternal age at delivery, yrs	1.0	1.0	1.0	0.29
Maternal Non-Hispanic white vs. others	1.3	1.0	1.8	0.08
Maternal above vs. less than high school education	0.9	0.6	1.3	0.62
Maternal not married vs. married	1.2	0.9	1.8	0.24
Prenatal tobacco use: Yes vs. No	1.5	0.9	2.3	0.09
Prenatal alcohol use: Yes vs. No	0.6	0.3	1.2	0.18
Prenatal marijuana use: Yes vs. No	0.9	0.5	1.7	0.72
Pre-pregnancy BMI, kg/m^2	1.0	1.0	1.0	0.76
MCHAT ~ SSRI, N=761				
Prenatal SSRI use Yes vs. No	1.0	0.2	5.8	0.99
Age at visit for the outcome, yrs	0.8	0.5	1.2	0.26
Child's sex: Female vs. Male	0.5	0.3	0.8	0.01
Prenatal depression diagnosis: Yes vs. No	0.8	0.3	1.9	0.56
Maternal age at delivery, yrs	1.0	1.0	1.1	0.12
Maternal Non-Hispanic white vs. others	0.8	0.5	1.4	0.50
Maternal above vs. less than high school education	0.4	0.2	0.6	<0.001
Maternal not married vs. married	1.9	1.2	3.2	0.01
Prenatal tobacco use: Yes vs. No	1.7	0.9	3.2	0.08
Prenatal alcohol use: Yes vs. No	1.1	0.4	3.4	0.83
Prenatal marijuana use: Yes vs. No	0.7	0.3	1.5	0.33
Pre-pregnancy BMI, kg/m^2	1.0	1.0	1.0	0.28

ASD, autism spectrum disorder; *BMI*, body mass index; *CBCL*, Child Behavior Checklist; *LCL*, lower confidence limit; *M-CHAT-R/F*, Modified Checklist for Autism in Toddlers-Revised with Follow-up; *OR*, odds ratio; *SRS-2*, Social Responsiveness Scale, Second Edition; *SSRI*, selective serotonin reuptake inhibitors; *UCL*, upper confidence limit