HHS Public Access

Author manuscript

Biol Psychiatry. Author manuscript; available in PMC 2022 August 15.

Published in final edited form as:

Biol Psychiatry. 2021 August 15; 90(4): 253–262. doi:10.1016/j.biopsych.2021.04.002.

Maternal Psychiatric Conditions, Treatment with SSRIs, and Neurodevelopmental Disorders

Jennifer L. Ames, PhD[1], **Christine Ladd-Acosta, PhD**[2], **M. Daniele Fallin, PhD**[2], **Yinge Qian, MS**[1], **Laura A. Schieve, PhD**[3], **Carolyn DiGuiseppi, MD, MPH, PhD**[4], **Li-Ching Lee, PhD**[5], **Eric P. Kasten, PhD**[6], **Guoli Zhou, MPH, MD, PhD**[6], **Jennifer Pinto-Martin, MPH, PhD**[7], **Ellen Howerton**[2], **Christopher L. Eaton, MD**[8], **Lisa A. Croen, PhD**[1]

[(1)]Division of Research, Kaiser Permanente, Oakland, CA

[(2)]Wendy Klag Center for Autism and Developmental Disabilities, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

[(3)]Centers for Disease Control and Prevention, Atlanta, GA

[(4)]Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, CO

[(5)]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

[(6)]Clinical and Translational Sciences Institute, Michigan State University, East Lansing, MI

[(7)]School of Nursing and Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

[(8)]The Permanente Medical Group, Kaiser Permanente Medical Center, San Francisco, CA

Abstract

Background: The present study aims to clarify relationships of maternal psychiatric conditions and selective serotonin reuptake inhibitors (SSRI) use during preconception and pregnancy with risk of neurodevelopmental disorders in offspring.

Methods: We used data from the Study to Explore Early Development, a multisite case-control study conducted in the United States among children born between 2003–2011. Final study group classifications of ASD (n=1367), DD (n= 1750), and general population controls (POP)(n=1671) were determined by an in-person standardized developmental assessment. Maternal psychiatric conditions and SSRI use during pregnancy were ascertained from both self-report and medical

Corresponding author: Jennifer L. Ames, PhD. Division of Research, Kaiser Permanente, 2000 Broadway, Oakland, CA, 94612. (Jennifer.l.ames@kp.org).

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, the National Institutes of Health, or the collaborating institutions.

AUTHOR DISCLOSURES

Dr. Pinto-Martin would like to acknowledge her work as an expert witness for Pfizer and Eli Lily related to a case on SSRIs and ASD. All other authors report no biomedical financial interests or potential conflicts of interest.

records. We used logistic regression to evaluate associations of ASD and DD (vs. POP) with maternal psychiatric condition and SSRI treatment in pregnancy. To reduce confounding by indication, we also examined SSRI associations in analyses restricted to mothers with psychiatric conditions during pregnancy.

Results: Psychiatric conditions and SSRI use during pregnancy were significantly more common among mothers of children with either ASD or DD than POP controls. Odds of ASD were similarly elevated among mothers with psychiatric conditions who did not use SSRIs during pregnancy (adjusted odds ratio (aOR)=1.81, 95% confidence interval (CI) 1.44–2.27) as in mothers who did use SSRIs (aOR=2.05, 95% CI 1.50–2.80). Among mothers with psychiatric conditions, SSRI use was not significantly associated with ASD in offspring (aOR=1.14, 95% CI 0.8–1.62). Primary findings for DD exhibited similar relationships to those observed with ASD.

Conclusions: Maternal psychiatric conditions, but not use of SSRIs during pregnancy, were associated with increased risk of neurodevelopmental disorders in offspring.

Keywords

Autism; SSRIs; antidepressants; psychiatric conditions; perinatal; developmental disorders; Antidepressants; Autism; Neurodevelopmental Disorders; Perinatal Exposure; Psychiatric Conditions; SSRIs

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by impairments in social communication, sensory processing, and behavior that begins in childhood and usually persists into adulthood. Over the last two decades, ASD prevalence has risen globally (1), including rapid increases in the United States where the prevalence now stands at 1 in 59 8-year-olds (2). Both genetic and environmental factors appear to shape ASD risk, though the mechanisms of their interplay remain elusive (3). Much research has focused on ASD's origins during gestation, when the developing brain may be particularly sensitive to environmental perturbations (3).

Selective serotonin reuptake inhibitors (SSRIs), commonly the first-line treatment for depression in the general adult population (4) but approved for a variety of psychiatric indications, are used by an estimated 6% of pregnant women in the United States (5–7) and can cross the placenta (8). Prenatal exposure to SSRIs has been linked to modest increases in risk of multiple adverse birth outcomes (9–13). Studies in animal models indicate that prenatal SSRI exposure may cause abnormal social-emotional behaviors in offspring (14, 15), suggesting that neurodevelopment may also be a sensitive endpoint in humans. Furthermore, the brain's serotonergic pathways, the target of SSRIs, are often atypical in individuals with ASD; clinical features associated with ASD include abnormal serotonin levels, disrupted biosynthesis and binding of the serotonin transporter protein, and rare variation in serotonin-related genes (16, 17). However, whether serotonergic disruption is a cause or correlate of ASD pathophysiology remains an open question.

To date, epidemiological studies of the potential adverse relationship of prenatal exposure to SSRIs and ASD symptoms have been inconclusive, largely due to the intractable correlation

between SSRIs and their psychiatric indications (18). Several studies have reported adverse relationships between SSRIs and ASD that often diminish or disappear after accounting for the mother's psychiatric condition (19–22) or when comparing siblings discordant on prenatal SSRI exposure (23–26). However, some of the largest studies to examine this relationship have found SSRIs to be associated with increased risk of ASD, albeit small, even after applying several bias reduction methods (27–32).

Women being treated for psychiatric symptoms must weigh complex and uncertain risks to themselves and their children when deciding to use SSRIs during pregnancy. More rigorous evidence on whether the treatment itself or the psychiatric disorder that is the indication for treatment is the etiologically relevant factor may improve clinical decision-making. The objective of this study was to replicate and extend earlier studies of maternal psychiatric conditions, prenatal SSRI exposure, and ASD risk using more refined data on maternal mental health and child ASD diagnostic profiles. We conducted our analysis using data from a large, geographically and demographically diverse US sample with relatively high SSRI use, reflecting modern trends. Additionally, our analyses focused on exposure during vulnerable developmental windows, risk heterogeneity by ASD subtypes, and specificity in comparison to other developmental delays and disorders (DD).

METHODS AND MATERIALS

Study Population

The Study to Explore Early Development (SEED) is a multi-site, case-control study of ASD and other DD in six sites across the United States: California, Colorado, Georgia, Maryland, North Carolina, and Pennsylvania (33). Briefly, eligible children were born between 2003–2006 (SEED 1) or 2008–2011 (SEED 2) and lived in a site catchment area at birth and study enrollment. The study enrolled three groups: children with ASD (cases), children with other DD such as language delay or intellectual disability (DD controls – details summarized in Schendel et al., 2012 (33)), and children from the general population (POP controls). Children with ASD and DD were recruited from educational and clinical settings that serve children with developmental disorders. Children in the POP group were recruited from randomly sampled state birth records at each study site. The institutional review boards for each site approved the study and all enrolled participants provided written informed consent for themselves and their children.

Outcome Assessment

We sampled a subset of children enrolled in SEED who had completed a multi-stage process, using gold standard clinical assessments, to determine their final study group classification (ASD, DD, or POP) (34). First, the primary caregiver (the biological mother for 99.5%) completed the Social Communication Questionnaire (SCQ) (35) about the child during the enrollment telephone call. Children who scored >=11 on the SCQ (36) or had a prior ASD diagnosis or special education placement regardless of their SCQ score were subsequently administered a comprehensive, in-person assessment that included the Autism Diagnostic Observation Schedule (ADOS) (37), the Autism Diagnostic Interview Revised (ADI-R) (38, 39), the Mullen Scales of Early Learning (MSEL) (40), and the Vineland

Adaptive Behavior Scales-Second Edition (VABS-II) (41). All other children were evaluated with the MSEL, followed by the VABS-II if the MSEL standard score was <78. Children in the final ASD group (n=1429) met ASD diagnostic criteria on the ADOS and either the full ASD diagnostic criteria on the ADI-R or one of three alternate criteria on the ADI-R, as detailed in Wiggins et al. (34) The ASD group was further subtyped by 1) the presence or absence of co-occurring intellectual disability (ID) defined by MSEL composite standard scores <=70; 2) their ADOS calibrated symptom severity score (mild/moderate, severe); 3) their history of developmental regression based on caregiver report of language or social regression on the ADI-R; and 4) having a sibling with ASD (simplex (none) or multiplex (one or more)) based on caregiver report.

Children with a final classification of DD (N=1850) were those who were identified from clinical or educational settings as having a neurodevelopmental disorder and who either scored <11 on the SCQ or who scored ≥11 but did not meet study criteria for ASD after the in-person assessment. They were further subtyped by the presence or absence of co-occurring ID defined by MSEL composite standard scores <=70. Children with a final classification of POP (N=1734) were those enrolled from sampling of birth certificate files who either scored <11 on the SCQ or scored ≥11 but did not meet ASD criteria after the in-person assessment.

Maternal Psychiatric History and SSRI Use

Maternal psychiatric disorders and use of SSRIs during pregnancy were ascertained from all participants in three ways: self-report in a telephone interview shortly after study enrollment (SEED Caregiver Interview), self-report on the SEED maternal medical history form, and abstraction of prenatal medical records. During the Caregiver Interview, the mother was queried about the timing, frequency, and names of medications she took, specifically for psychiatric conditions, from 3 months before conception through the end of pregnancy. On the maternal medical history form, the mother was asked to specify whether a doctor had ever diagnosed her with any of the following conditions: attention-deficit/hyperactivity disorder (ADHD), anxiety disorder, bipolar disorder, depression, eating disorder, obsessive compulsive disorder, personality disorder, schizophrenia, self-injuring behavior, sleep disorder, suicide attempt, or other condition not listed. For each condition, she was asked the age of onset and whether she had the condition during the pregnancy. Psychiatric diagnoses and the names and timing of medications used during pregnancy were abstracted from her medical records. We coded a mother as having a psychiatric condition and/or as an SSRI user if documented in the Caregiver Interview, maternal medical history or medical records. Child exposure to maternal psychiatric conditions and SSRIs was examined in 5 prenatal periods: 3 months pre-conception, each trimester, and anytime during pregnancy.

Covariates

We considered *a priori* several factors associated with ASD or maternal psychiatric conditions in previous work. We pared down the final adjustment set to covariates associated with child outcomes and not considered intermediates in the pathways of interest;

these included maternal race/ethnicity, education level, age at delivery, and smoking, and household income during pregnancy.

Statistical Analyses

The final analytic sample included children with completed maternal psychiatric and medication information available in all three sources (Caregiver Interview, maternal medical history, and medical record data). We further excluded a small subset of participants (4.5%) with missing sociodemographic information. Using SAS 9.3, we examined crude differences in the distribution of demographic characteristics, maternal psychiatric conditions, and prenatal SSRI use across the child outcome groups using chi-square statistics.

To disentangle the independent associations of maternal psychiatric condition ("Psy") and SSRI use with odds of child ASD, our primary analysis evaluated four separate logistic regression models. Using a reference group of children who were never exposed to either factor prenatally (Psy No), the first three models examined 1) the association of ASD with prenatal exposure to maternal psychiatric condition, regardless of SSRI exposure (Psy Yes); 2) the association of ASD with prenatal exposure to maternal psychiatric condition but not SSRIs (Psy Yes + SSRI No); and 3) the joint association of ASD with prenatal exposure to both maternal psychiatric condition and SSRIs (Psy Yes + SSRI Yes). In the fourth model, we examined the association of ASD with prenatal exposure to SSRIs in a sample restricted to children of mothers with a psychiatric condition during pregnancy ((Psy Yes + SSRI Yes) vs. (Psy Yes + SSRI No)).

The above analytical procedures were repeated for DD vs. POP comparisons.

Secondary analyses included stratification by ASD severity, co-occurring ID, a history of developmental regression, and family history of ASD. We did not correct for multiple comparisons.

RESULTS

The final analytic sample (N=4788) comprised 1,367 children with ASD, 1,750 with DD, and 1,671 POP controls (Supplementary eTable 1). Characteristics of the child, mother and household, most of which differed between groups, are shown in Table 1.

Approximately one third of mothers in the sample had a psychiatric condition before or during pregnancy (Table 2); 90% of those with a psychiatric condition were diagnosed before the start of pregnancy. Depression was the most prevalent followed by anxiety in all study groups. Mothers of children with either ASD or DD were more likely than mothers of children in the POP group to have 2+ psychiatric conditions (19% and 17%, respectively, vs. 11%; $p<0.001$).

The frequencies of any antidepressant use and SSRI use anytime during preconception or pregnancy were higher among mothers of children with ASD or DD than among mothers of POP controls (Table 2). SSRIs accounted for greater than 85% of antidepressants used, with Sertraline and Fluoxetine used most often. One quarter of mothers with a psychiatric condition used SSRIs during pre-conception and/or pregnancy (Table 3). Most SSRI users

during pregnancy had initiated SSRI use before the start of pregnancy (77%). Mothers with 2+ psychiatric conditions were more likely to use SSRIs than mothers with one condition (Supplementary eTable 2). The most common psychiatric conditions among SSRI users were depression (91%) and anxiety (64%).

The adjusted odds of having a child with ASD were nearly 2-fold higher among mothers with a psychiatric condition during pregnancy, regardless of SSRI use, than among mothers without a psychiatric condition (none of whom used SSRIs, by definition) (Psy Yes vs. Psy No): adjusted odds ratio (aOR)=1.93, 95% confidence interval (CI) 1.59 – 2.34) (Table 4). Higher odds of ASD were also observed among mothers with psychiatric conditions in stratified analyses considering, separately, mothers who did not use SSRIs during pregnancy ((Psy Yes + SSRI No) vs (Psy No): aOR=1.81, 95% CI 1.44–2.27) and mothers who did use SSRIs anytime during pregnancy ((Psy Yes + SSRI Yes) vs. (Psy No): aOR=2.05, 95% CI 1.50–2.80). When we restricted the analysis to mothers with a psychiatric condition, we found no evidence of association between SSRI use anytime during pregnancy and ASD ((Psy Yes + SSRI Yes) vs. (Psy Yes + SSRI No): aOR=1.14, 95% CI 0.80–1.62). These relationships were consistent for exposure across the pre-conception period and all trimesters of pregnancy.

Among mothers with psychiatric conditions, the associations of prenatal SSRI exposure were consistently null in analyses of ASD subtypes defined by autistic symptom severity, ID status, regression history, and family history (Supplementary Figures 1-4). However, associations with maternal psychiatric condition suggested risk heterogeneity across some ASD subtypes. Specifically, associations of maternal psychiatric condition both with and without SSRI treatment were strongest among children with ASD without co-occurring ID and in multiplex families (Supplementary Figures 2 and 4).

Maternal psychiatric condition and SSRI use generally exhibited similar relationships with DD as with ASD (Table 4), with some exceptions. Maternal psychiatric conditions during preconception and pregnancy, with and without SSRI use, were associated with DD, though point estimates were larger for the joint exposure. In analyses restricted to mothers with psychiatric conditions, SSRI use during preconception was associated with higher odds of having a child with DD (aOR=1.69, 95% CI 1.21–2.35); SSRI use by trimester and anytime during pregnancy also showed modestly higher odds of DD, though confidence intervals contained the null. In all time windows, maternal psychiatric conditions, particularly when combined with SSRI use, were associated with higher odds of DD without co-occurring ID but not DD with co-occurring ID (Supplementary Figure 5). In models restricted to mothers with psychiatric conditions, SSRI use also trended with higher odds of DD without co-occurring ID (SSRI use anytime during pregnancy, aOR=1.47, 95% CI 1.03–2.09) but not DD with co-occurring ID. However, confidence intervals in these secondary analyses of DD were wide and overlapping.

DISCUSSION

Our results, from a large and diverse US sample, suggest that mothers with psychiatric conditions during pregnancy, irrespective of SSRI use, had elevated odds of having a child

with ASD or DD. Maternal psychiatric conditions during pregnancy were most strongly associated with subtypes of ASD and DD without co-occurring ID. Among mothers with psychiatric conditions during pregnancy, SSRI use was not related to ASD, suggesting that SSRIs may not raise odds of ASD independently of their psychiatric indications; however, we observed that odds of DD, particularly DD without co-occurring ID, were higher in children of mothers who used SSRIs during pre-conception and pregnancy.

Our findings of no association between prenatal SSRI exposure and ASD are consistent with the conclusions of several large, population-based studies that specifically address confounding by indication (19–26, 42). To strengthen causal inference, four of these studies included sibling analyses which control for unmeasured or imperfectly measured maternal factors, such as genetics or psychiatric severity (23–26). However, reflecting the mixed evidence of this research area, our findings also contradict several other large studies conducted in Sweden,(30, 43) the Netherlands (44), California (31, 32), Canada (29), and Denmark (27, 28). These positive findings in other studies persisted even after efforts to reduce confounding by indication through adjustment for maternal psychiatric condition (29, 31, 43, 44), restriction to mothers with psychiatric conditions (27–30, 32), and propensity weighting methods (30). In evaluating these methods, a recent systematic review of the literature determined that study designs using SSRI-unexposed mothers with psychiatric conditions (as was done in the present study) and/or siblings as comparators afford the most rigorous approaches for circumventing issues of residual confounding by psychiatric indication (18). The body of evidence produced from these two methods generally support no association between prenatal SSRI exposure and ASD (18).

Associations between ASD and maternal psychiatric conditions preceding or during pregnancy (20, 45, 46), including depression (24, 43, 44, 47), schizophrenia (48, 49), anxiety (50), and personality disorders (48), are commonly reported in the literature. The prevalence of psychiatric conditions in families of children with ASD is substantially higher than in the general population (51, 52). Given the significant genetic overlap between various psychiatric conditions and ASD, heritability likely contributes to these relationships (53–55). Shared common genetic risk is also suggested by our finding that maternal psychiatric conditions were more strongly associated with ASD in multiplex families than in simplex families. Future analyses that take into account maternal and child genetic information may be able to determine whether this finding reflects overlap in genetic risk for psychiatric conditions and ASD or heightened psychiatric morbidity associated with raising an earlier-born child with ASD (56).

Relationships between DD and prenatal SSRIs were overall similar to those observed with ASD, and in agreement with previous null reports of prenatal SSRI use and ADHD (21, 25, 42), DD (32, 57), and ID (27, 58). While secondary findings suggest that maternal SSRI use may be associated with increased odds of DD without ID, the confidence intervals for DD with and without ID overlapped. Due to the large number of tests conducted in secondary analyses, it is also possible that this significant finding is due to chance. Previous studies have observed associations between prenatal SSRI exposure and specific types of DD, including motor (32, 59) and speech/language delays (57). In our study, the DD group encompassed heterogenous diagnoses; larger sample sizes of specific DD diagnoses could

help clarify these findings. Studies that examine genetic susceptibility for ASD and DD, as well as genes involved in SSRI metabolism, could also provider further insights and possibly identify genetic subgroups sensitive to prenatal SSRI exposure.

For both ASD and DD outcomes, associations with maternal psychiatric conditions were stronger for child diagnostic subgroups without co-occurring ID than for those with co-occurring ID. Similar relationships between maternal psychiatric conditions and ASD without co-occurring ID have been noted in other studies (30, 43, 46), perhaps indicating a distinct etiologic class compared to conditions with ID, which warrants further research.

The methodological rigor of the present study goes beyond what has been possible in studies making use of national registry data. Our study benefitted from clinically validated diagnoses of neurodevelopmental disorders and detailed data on pre-conception and pregnancy exposures and potential confounders. Combining both medical records and self-reported data allowed for more accurate characterization of psychiatric history and medication use during pregnancy, overcoming the limitations of ascertaining these exposures from exclusively dispensing data or self-report as done in earlier work. Unlike previous studies focused on maternal depressive disorders, we inspected a wider array of SSRI indications. Including children with DD further allowed for evaluation of the specificity of impact of SSRI use on non-ASD neurodevelopmental endpoints. While this study focused specifically on SSRIs, associations with the use of alternative, serotogenically-active antidepressants may be a useful topic in future investigations (60).

The SEED population, representing six different geographic locations across the US, is large and sociodemographically diverse. To enhance generalizability, participants with ASD and DD were recruited from various settings that provide services to children with disabilities. Nevertheless, as discussed in earlier work, not all invited families enrolled in the study and response rates differed between cases and controls (33). However, an analysis that compared characteristics of responders and non-responders at one site found that, although maternal age, education, and race/ethnicity predicted study participation, risk factor analyses adjusted for these sociodemographic variables were generally robust to the impact of non-response bias (61). Further, previous work has demonstrated that completion rates of SEED's Caregiver Interview and in-person assessment across outcome groups were not associated with sociodemographic factors (62). Additionally, rates of maternal SSRI use in the SEED sample were comparable to other US estimates (5–7), mitigating concerns about selection bias in participation.

Incorporating data on self-reported maternal psychiatric conditions and SSRI use raises the possibility of exposure misclassification. However, combining these data with information recorded in prenatal medical records reduced bias due to poor recall of exposures before and during pregnancy. Our analytic strategy of examining the impact of prenatal exposure to SSRIs among mothers with psychiatric histories mitigated but did not completely resolve confounding by condition severity. We did not have detailed information on medication dosing or symptoms during pregnancy to parse this bias; however, there was some evidence that mothers of children with ASD and DD, who were more likely than mothers of children in the POP group to use SSRIs, were also more likely to have multiple psychiatric diagnoses,

a crude proxy for condition severity. Power was also limited for trimester-specific analyses among some subgroups. Future planned SEED analyses will examine maternal genetic risk markers of psychiatric conditions to better disentangle the impacts of maternal condition severity and higher propensity for SSRI treatment on ASD and DD outcomes.

CONCLUSION

These results suggest that prenatal exposure to SSRIs is not associated with increased odds of ASD among children of women with a psychiatric indication for treatment. However, in secondary analyses, we noted significant associations between prenatal SSRI exposure and DD without co-occurring ID, a possible false-positive finding that needs confirmation in future work. Clinical decision-making regarding the continuation of SSRI treatment during pregnancy must carefully weigh the potential risk to the baby against the psychiatric risk to the mother. Incorporating maternal and child genetic information into future analyses will further our understanding of the independent and joint effects of maternal psychiatric conditions and their treatments during pregnancy on child neurodevelopmental disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

This study was supported by six cooperative agreements from the Centers for Disease Control and Prevention: Cooperative Agreement Number U10DD000180, Colorado Department of Public Health; Cooperative Agreement Number U10DD000181, Kaiser Foundation Research Institute (CA); Cooperative Agreement Number U10DD000182, University of Pennsylvania; Cooperative Agreement Number U10DD000183, Johns Hopkins University; Cooperative Agreement Number U10DD000184, University of North Carolina at Chapel Hill; and Cooperative Agreement Number U10DD000498, Michigan State University and the National Institutes of Health grant R01HD087915. We thank the SEED Data Coordinating Center team at the Clinical and Translational Sciences Institute of Michigan State University for their support throughout this study.

Abbreviations:

ASD	Autism Spectrum Disorder
DD	Developmental Delay or Disorder
ID	Intellectual Disability
POP	General Population
SEED	Study to Explore Early Development
SSRI	Selective serotonin reuptake inhibitors

REFERENCES

1. Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcin C, et al. (2012): Global prevalence of autism and other pervasive developmental disorders. Autism Res. 5:160–179. [PubMed: 22495912]
2. Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, et al. (2018): Prevalence of autism spectrum disorder among children aged 8 years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2014. MMWR Surveill Summ. 67:1–23.

3. Lyall K, Croen L, Daniels J, Fallin MD, Ladd-Acosta C, Lee BK, et al. (2017): The changing epidemiology of autism spectrum disorders. Annu Rev Public Health. 38:81–102. [PubMed: 28068486]
4. Association AP (2019): Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts, American Psychological Association, Guideline Development Panel for the Treatment of Depressive Disorders. Washington, DC.
5. Alwan S, Reefhuis J, Rasmussen SA, Friedman JM, National Birth Defects Prevention S (2011): Patterns of antidepressant medication use among pregnant women in a United States population. J Clin Pharmacol. 51:264–270. [PubMed: 20663997]
6. Ailes EC, Simeone RM, Dawson AL, Petersen EE, Gilboa SM (2016): Using insurance claims data to identify and estimate critical periods in pregnancy: An application to antidepressants. Birth Defects Res A Clin Mol Teratol. 106:927–934. [PubMed: 27891779]
7. Andrade SE, Reichman ME, Mott K, Pitts M, Kieswetter C, Dinatale M, et al. (2016): Use of selective serotonin reuptake inhibitors (SSRIs) in women delivering liveborn infants and other women of child-bearing age within the U.S. Food and Drug Administration's Mini-Sentinel program. Arch Womens Ment Health. 19:969–977. [PubMed: 27178125]
8. Rampono J, Simmer K, Ilett KF, Hackett LP, Doherty DA, Elliot R, et al. (2009): Placental transfer of SSRI and SNRI antidepressants and effects on the neonate. Pharmacopsychiatry. 42:95–100. [PubMed: 19452377]
9. Reefhuis J, Devine O, Friedman JM, Louik C, Honein MA, Study NBDP (2015): Specific SSRIs and birth defects: Bayesian analysis to interpret new data in the context of previous reports. BMJ. 351:h3190. [PubMed: 26156519]
10. Alwan S, Friedman JM, Chambers C (2016): Safety of selective serotonin reuptake inhibitors in pregnancy: A review of current evidence. CNS Drugs. 30:499–515. [PubMed: 27138915]
11. Yonkers KA, Wisner KL, Stewart DE, Oberlander TF, Dell DL, Stotland N, et al. (2009): The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. Gen Hosp Psychiatry. 31:403–413. [PubMed: 19703633]
12. Colvin L, Slack-Smith L, Stanley FJ, Bower C (2012): Early morbidity and mortality following in utero exposure to selective serotonin reuptake inhibitors: a population-based study in Western Australia. CNS Drugs. 26:e1–14. [PubMed: 22712699]
13. Tuccori M, Testi A, Antonioli L, Fornai M, Montagnani S, Ghisu N, et al. (2009): Safety concerns associated with the use of serotonin reuptake inhibitors and other serotonergic/noradrenergic antidepressants during pregnancy: a review. Clin Ther. 31 Pt 1:1426–1453. [PubMed: 19698902]
14. Gemmel M, Bogi E, Ragan C, Hazlett M, Dubovicky M, van den Hove DL, et al. (2018): Perinatal selective serotonin reuptake inhibitor medication (SSRI) effects on social behaviors, neurodevelopment and the epigenome. Neurosci Biobehav Rev. 85:102–116. [PubMed: 28472631]
15. Yu W, Yen YC, Lee YH, Tan S, Xiao Y, Lokman H, et al. (2019): Prenatal selective serotonin reuptake inhibitor (SSRI) exposure induces working memory and social recognition deficits by disrupting inhibitory synaptic networks in male mice. Mol Brain. 12:29. [PubMed: 30935412]
16. Pardo CA, Eberhart CG (2007): The neurobiology of autism. Brain Pathol. 17:434–447. [PubMed: 17919129]
17. Anderson BM, Schnetz-Boutaud NC, Bartlett J, Wotawa AM, Wright HH, Abramson RK, et al. (2009): Examination of association of genes in the serotonin system to autism. Neurogenetics. 10:209–216. [PubMed: 19184136]
18. Morales DR, Slattery J, Evans S, Kurz X (2018): Antidepressant use during pregnancy and risk of autism spectrum disorder and attention deficit hyperactivity disorder: systematic review of observational studies and methodological considerations. BMC Med. 16:6. [PubMed: 29332605]
19. Clements CC, Castro VM, Blumenthal SR, Rosenfield HR, Murphy SN, Fava M, et al. (2015): Prenatal antidepressant exposure is associated with risk for attention-deficit hyperactivity disorder but not autism spectrum disorder in a large health system. Mol Psychiatry. 20:727–734. [PubMed: 25155880]
20. Hviid A, Melbye M, Pasternak B (2013): Use of selective serotonin reuptake inhibitors during pregnancy and risk of autism. N Engl J Med. 369:2406–2415. [PubMed: 24350950]

21. Malm H, Brown AS, Gissler M, Gyllenberg D, Hinkka-Yli-Salomaki S, McKeague IW, et al. (2016): Gestational exposure to selective serotonin reuptake inhibitors and offspring psychiatric disorders: a national register-based study. J Am Acad Child Adolesc Psychiatry. 55:359–366. [PubMed: 27126849]
22. Viktorin A, Uher R, Reichenberg A, Levine SZ, Sandin S (2017): Autism risk following antidepressant medication during pregnancy. Psychol Med. 47:2787–2796. [PubMed: 28528584]
23. Brown HK, Ray JG, Wilton AS, Lunsky Y, Gomes T, Vigod SN (2017): Association between serotonergic antidepressant use during pregnancy and autism spectrum disorder in children. JAMA. 317:1544–1552. [PubMed: 28418480]
24. Hagberg KW, Robijn AL, Jick S (2018): Maternal depression and antidepressant use during pregnancy and the risk of autism spectrum disorder in offspring. Clin Epidemiol. 10:1599–1612. [PubMed: 30464639]
25. Sujan AC, Rickert ME, Oberg AS, Quinn PD, Hernandez-Diaz S, Almqvist C, et al. (2017): Associations of maternal antidepressant use during the first trimester of pregnancy with preterm birth, small for gestational age, autism spectrum disorder, and attention-deficit/hyperactivity disorder in offspring. JAMA. 317:1553–1562. [PubMed: 28418479]
26. Sorensen MJ, Gronborg TK, Christensen J, Parner ET, Vestergaard M, Schendel D, et al. (2013): Antidepressant exposure in pregnancy and risk of autism spectrum disorders. Clin Epidemiol. 5:449–459. [PubMed: 24255601]
27. Liu X, Agerbo E, Ingstrup KG, Musliner K, Meltzer-Brody S, Bergink V, et al. (2017): Antidepressant use during pregnancy and psychiatric disorders in offspring: Danish nationwide register based cohort study. BMJ. 358:j3668. [PubMed: 28877907]
28. Gidaya NB, Lee BK, Burstyn I, Yudell M, Mortensen EL, Newschaffer CJ (2014): In utero exposure to selective serotonin reuptake inhibitors and risk for autism spectrum disorder. J Autism Dev Disord. 44:2558–2567. [PubMed: 24803368]
29. Boukhris T, Sheehy O, Mottron L, Berard A (2016): Antidepressant use during pregnancy and the risk of autism spectrum disorder in children. JAMA Pediatr. 170:117–124. [PubMed: 26660917]
30. Rai D, Lee BK, Dalman C, Newschaffer C, Lewis G, Magnusson C (2017): Antidepressants during pregnancy and autism in offspring: population based cohort study. BMJ. 358:j2811. [PubMed: 28724519]
31. Croen LA, Grether JK, Yoshida CK, Odouli R, Hendrick V (2011): Antidepressant use during pregnancy and childhood autism spectrum disorders. Arch Gen Psychiatry. 68:1104–1112. [PubMed: 21727247]
32. Harrington RA, Lee LC, Crum RM, Zimmerman AW, Hertz-Picciotto I (2014): Prenatal SSRI use and offspring with autism spectrum disorder or developmental delay. Pediatrics. 133:e1241–1248. [PubMed: 24733881]
33. Schendel DE, Diguiseppi C, Croen LA, Fallin MD, Reed PL, Schieve LA, et al. (2012): The Study to Explore Early Development (SEED): a multisite epidemiologic study of autism by the Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) network. J Autism Dev Disord. 42:2121–2140. [PubMed: 22350336]
34. Wiggins LD, Reynolds A, Rice CE, Moody EJ, Bernal P, Blaskey L, et al. (2015): Using standardized diagnostic instruments to classify children with autism in the study to explore early development. J Autism Dev Disord. 45:1271–1280. [PubMed: 25348175]
35. Rutter M, Bailey A, Lord C (2003a): SCQ: Social Communication Questionnaire. Los Angeles, CA: Western Psychological Services.
36. Wiggins LD, Bakeman R, Adamson LB, Robins DL (2007): The Utility of the Social Communication Questionnaire in Screening for Autism in Children Referred for Early Intervention. Focus on Autism and Other Developmental Disabilities. 22:33–38.
37. Lord C, Risi S, Lambrecht L, Cook EH Jr., Leventhal BL, DiLavore PC, et al. (2000): The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. J Autism Dev Disord. 30:205223.
38. Lord C, Rutter M, Le Couteur A (1994): Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J Autism Dev Disord. 24:659–685. [PubMed: 7814313]

39. Rutter M, Le Couteur A, Lord C (2003b): ADI-R: The Autism Diagnotic InterviewRevised. Los Angeles, CA: Western Psychological Services.
40. Mullen EM (1995): Mullen scales of early learning. Circle Pines, MN: American Guidance Service, Inc.
41. Sparrow S, Cichetti D, Balla D (2005): Vineland Adaptive Behavior Scales (2nd ed). Circle Pines, MN: American Guidance Service.
42. Castro VM, Kong SW, Clements CC, Brady R, Kaimal AJ, Doyle AE, et al. (2016): Absence of evidence for increase in risk for autism or attention-deficit hyperactivity disorder following antidepressant exposure during pregnancy: a replication study. Transl Psychiatry. 6:e708. [PubMed: 26731445]
43. Rai D, Lee BK, Dalman C, Golding J, Lewis G, Magnusson C (2013): Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. BMJ. 346:f2059. [PubMed: 23604083]
44. El Marroun H, White TJ, van der Knaap NJ, Homberg JR, Fernandez G, Schoemaker NK, et al. (2014): Prenatal exposure to selective serotonin reuptake inhibitors and social responsiveness symptoms of autism: population-based study of young children. Br J Psychiatry. 205:95–102. [PubMed: 25252317]
45. Lauritsen MB, Pedersen CB, Mortensen PB (2005): Effects of familial risk factors and place of birth on the risk of autism: a nationwide register-based study. J Child Psychol Psychiatry. 46:963–971. [PubMed: 16108999]
46. Wiggins LD, Rubenstein E, Daniels J, DiGuiseppi C, Yeargin-Allsopp M, Schieve LA, et al. (2019): A phenotype of childhood autism is associated with preexisting maternal anxiety and depression. J Abnorm Child Psychol. 47:731–740. [PubMed: 30128718]
47. Piven J, Palmer P (1999): Psychiatric disorder and the broad autism phenotype: evidence from a family study of multiple-incidence autism families. Am J Psychiatry. 156:557–563. [PubMed: 10200734]
48. Daniels JL, Forssen U, Hultman CM, Cnattingius S, Savitz DA, Feychting M, et al. (2008): Parental psychiatric disorders associated with autism spectrum disorders in the offspring. Pediatrics. 121:e1357–1362. [PubMed: 18450879]
49. Piven J, Chase GA, Landa R, Wzorek M, Gayle J, Cloud D, et al. (1991): Psychiatric disorders in the parents of autistic individuals. J Am Acad Child Adolesc Psychiatry. 30:471–478. [PubMed: 1829081]
50. Duvekot J, van der Ende J, Constantino JN, Verhulst FC, Greaves-Lord K (2016): Symptoms of autism spectrum disorder and anxiety: shared familial transmission and cross-assortative mating. J Child Psychol Psychiatry. 57:759–769. [PubMed: 26714925]
51. Bolton PF, Pickles A, Murphy M, Rutter M (1998): Autism, affective and other psychiatric disorders: patterns of familial aggregation. Psychol Med. 28:385–395. [PubMed: 9572095]
52. Larsson HJ, Eaton WW, Madsen KM, Vestergaard M, Olesen AV, Agerbo E, et al. (2005): Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status. Am J Epidemiol. 161:916–925; discussion 926–918. [PubMed: 15870155]
53. Solberg BS, Zayats T, Posserud MB, Halmoy A, Engeland A, Haavik J, et al. (2019): Patterns of psychiatric comorbidity and genetic correlations provide new insights into differences between attention-deficit/hyperactivity disorder and autism spectrum disorder. Biol Psychiatry.
54. Cross-Disorder Group of the Psychiatric Genomics C (2013): Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet. 381:1371–1379. [PubMed: 23453885]
55. Carroll LS, Owen MJ (2009): Genetic overlap between autism, schizophrenia and bipolar disorder. Genome Med. 1:102. [PubMed: 19886976]
56. Zablotsky B, Anderson C, Law P (2013): The association between child autism symptomatology, maternal quality of life, and risk for depression. J Autism Dev Disord. 43:1946–1955. [PubMed: 23263770]
57. Brown AS, Gyllenberg D, Malm H, McKeague IW, Hinkka-Yli-Salomaki S, Artama M, et al. (2016): Association of selective serotonin reuptake inhibitor exposure during pregnancy with

speech, scholastic, and motor disorders in offspring. JAMA Psychiatry. 73:1163–1170. [PubMed: 27732704]

58. Viktorin A, Uher R, Kolevzon A, Reichenberg A, Levine SZ, Sandin S (2017): Association of antidepressant medication use during pregnancy with intellectual disability in offspring. JAMA Psychiatry. 74:1031–1038. [PubMed: 28700807]
59. Pedersen LH, Henriksen TB, Olsen J (2010): Fetal exposure to antidepressants and normal milestone development at 6 and 19 months of age. Pediatrics. 125:e600–608. [PubMed: 20176667]
60. Sujan AC, Oberg AS, Quinn PD, D'Onofrio BM (2019): Annual Research Review: Maternal antidepressant use during pregnancy and offspring neurodevelopmental problems - a critical review and recommendations for future research. J Child Psychol Psychiatry. 60:356–376. [PubMed: 30515808]
61. Schieve LA, Harris S, Maenner MJ, Alexander A, Dowling NF (2018): Assessment of demographic and perinatal predictors of non-response and impact of non-response on measures of association in a population-based case control study: findings from the Georgia Study to Explore Early Development. Emerg Themes Epidemiol. 15:12. [PubMed: 30147744]
62. DiGuiseppi CG, Daniels JL, Fallin DM, Rosenberg SA, Schieve LA, Thomas KC, et al. (2016): Demographic profile of families and children in the Study to Explore Early Development (SEED): Case-control study of autism spectrum disorder. Disabil Health J 9:544–551. [PubMed: 26917104]

Table 1

Characteristics of the Study Population, Study to Explore Early Development (SEED), 2002–2006 and 2008–2011 Births (N=4788).

	ASD (N=1367)	DD (N=1750)	POP (N=1671)	ASD vs POP	DD vs POP
Variable	**n (%)**	**n (%)**	**n (%)**	**p-value**	**p-value**
Child Sex (Male)	1115 (81.6)	1158 (66.2)	878 (52.5)	<0.001	<0.001
Gestational Age					
Early Preterm (<=33wks)	83 (6.1)	174 (9.9)	49 (2.9)	<0.001	<0.001
Preterm (>33wks & <37wks)	134 (9.8)	222 (12.7)	117 (7.0)		
Term (>=37wks)	1150 (84.1)	1354 (77.4)	1505 (90.1)		
Cesarean-Section Delivery	564 (41.3)	689 (39.4)	544 (32.6)	<0.001	<0.001
Plurality					
Singleton	1266 (92.6)	1623 (92.7)	1598 (95.6)	<0.001	<0.001
Multiple	101 (7.4)	127 (7.3)	73 (4.4)		
Maternal Age (years)					
< 25	167 (12.2)	266 (15.2)	173 (10.4)	0.03	<0.001
25–29	341 (24.9)	392 (22.4)	392 (23.5)		
30–34	484 (35.4)	588 (33.6)	629 (37.6)		
35–39	287 (21.0)	398 (22.7)	398 (23.8)		
>=40	88 (6.4)	106 (6.1)	79 (4.7)		
Paternal Age (years)					
< 25	104 (7.6)	167 (9.5)	94 (5.6)	<0.001	<0.001
25–29	229 (16.8)	307 (17.5)	284 (17.0)		
30–34	393 (28.7)	515 (29.4)	542 (32.4)		
35–39	336 (24.6)	426 (24.3)	485 (29.0)		
>=40	305 (22.3)	335 (19.1)	266 (15.9)		
Maternal Race					
White	797 (58.3)	1097 (62.7)	1239 (74.1)	<0.001	<0.001
Black	321 (23.5)	389 (22.2)	232 (13.9)		
Asian	115 (8.4)	71 (4.1)	90 (5.4)		
Hispanic	69 (5.1)	91 (5.2)	41 (2.5)		
Other	65 (4.8)	102 (5.8)	69 (4.1)		
Maternal Education					
High School & Less	177 (12.9)	308 (17.6)	153 (9.2)	<0.001	<0.001
College	888 (65.0)	1001 (57.2)	952 (57.0)		
Graduate School	302 (22.1)	441 (25.2)	566 (33.9)		
Family Income (During Pregnancy)					
<50K	549 (40.2)	739 (42.2)	447 (26.8)	<0.001	<0.001
50–90K	412 (30.1)	503 (28.7)	559 (33.5)		
>90K	406 (29.7)	508 (29.0)	665 (39.8)		
Maternal Smoking (During Preconception + Pregnancy)					

Variable	ASD (N=1367) n (%)	DD (N=1750) n (%)	POP (N=1671) n (%)	ASD vs POP p-value	DD vs POP p-value
Yes	226 (16.53)	246 (14.06)	168 (10.1)	<0.001	<0.001
No	1141 (83.47)	1504 (85.94)	1503 (89.9)		
Maternal Hypertension (During Pregnancy)					
Yes	231 (16.90)	179 (10.23)	186 (11.1)	<0.001	<0.001
No	951 (69.57)	871 (49.77)	1277 (76.4)		
Missing	185 (13.53)	700 (40.00)	208 (12.4)		
Maternal History of Infertility					
Yes	267 (19.53)	296 (16.91)	258 (15.4)	0.009	0.002
No	1049 (76.74)	1355 (77.43)	1357 (81.2)		
Missing	51 (3.73)	99 (5.66)	56 (3.4)		
SEED Years					
SEED1	628 (45.94)	915 (52.29)	867 (51.9)	0.001	0.81
SEED2	739 (54.06)	835 (47.71)	804 (48.1)		

ASD=Autism spectrum disorder; DD=Developmental disorder; n=Number; POP=Population controls;

Table 2

Frequency of Maternal Psychiatric Conditions and Antidepressant Use During Pre-Conception and/or Pregnancy, Study to Explore Early Development, 2002–2006 and 2008–2011 Births.

	ASD (n=1367)	DD (n=1750)	POP (n=1671)	ASD vs POP	DD vs POP
	n (%)	n (%)	n (%)	p-value	p-value
Psychiatric Condition	500 (36.6)	593 (33.9)	455 (27.2)	<0.001	<0.001
ADHD	52 (3.8)	60 (3.4)	30 (1.8)	0.001	0.003
Anxiety Disorder	218 (15.9)	275 (15.7)	170 (10.2)	<0.001	<0.001
Bipolar Disorder	49 (3.6)	64 (3.7)	33 (2.0)	0.007	0.003
Depression	372 (27.2)	418 (23.9)	321 (19.2)	<0.001	0.001
Eating Disorder	35 (2.6)	44 (2.5)	45 (2.7)	0.82	0.74
Obsessive-Compulsive Disorder	23 (1.7)	32 (1.8)	14 (0.8)	0.03	0.01
Personality Disorder	9 (0.7)	14 (0.8)	6 (0.4)	0.24	0.09
Schizophrenia	5 (0.4)	7 (0.4)	2 (0.1)	0.25	0.11
Sleep Disorder	109 (8.0)	116 (6.6)	68 (4.1)	<0.001	0.001
Self-Injuring Behavior	21 (1.5)	20 (1.1)	21 (1.3)	0.51	0.76
Suicide Attempt	49 (3.6)	60 (3.4)	27 (1.6)	0.001	0.001
One Psychiatric Condition	245 (17.9)	294 (16.8)	276 (16.5)	0.31	0.82
2+ Psychiatric Conditions	255 (18.7)	299 (17.1)	179 (10.7)	<0.001	<0.001
Antidepressant Use					
Any Antidepressant	148 (10.8)	185 (10.6)	120 (7.2)	<0.001	0.001
SSRI	128 (9.4)	171 (9.8)	99 (5.9)	<0.001	<0.001
Citalopram	16 (1.2)	22 (1.3)	15 (0.9)	0.46	0.31
Escitalopram	17 (1.2)	20 (1.1)	10 (0.6)	0.06	0.09
Fluoxetine	29 (2.1)	36 (2.1)	21 (1.3)	0.06	0.07
Fluvoxamine	1 (0.1)	0 (0.0)	1 (0.1)	1.00	0.49
Paroxetine	18 (1.3)	20 (1.1)	8 (0.5)	0.01	0.03
Sertraline	49 (3.6)	77 (4.4)	40 (2.4)	0.05	0.001
Name Unknown	20 (1.5)	18 (1.0)	11 (0.7)	0.03	0.24
MAO Inhibitor	0 (0.0)	0 (0.0)	0 (0.0)		
TCA	3 (0.2)	2 (0.1)	3 (0.2)	0.81	0.62
Serotonin Modulator	9 (0.7)	9 (0.5)	5 (0.3)	0.15	0.32
Selective Serotonin	18 (1.3)	14 (0.8)	23 (1.4)	0.89	0.10
Miscellaneous	3 (0.2)	3 (0.2)	0 (0.0)	0.06	0.25

ADHD=Attention-deficit/hyperactivity disorder; ASD=Autism spectrum disorder; DD=Developmental disorder; MAO=Monoamine oxidase; n=Number; POP=Population controls; SSRI=Selective serotonin reuptake inhibitor; TCA=Tricyclic antidepressant

Table 3

- Frequency of Maternal SSRI Use During Pre-conception and/or Pregnancy among Women with Any Psychiatric Disorder, Study to Explore Early Development, 2002–2006 and 2008–2011 Births.

SSRI Use[a]	ASD	DD	POP	ASD vs POP	DD vs POP
	n (%[b])	n (%[b])	n (%[b])	p-value	p-value
Any Psychiatric Condition	128 (25.6)	167 (28.2)	94 (20.7)	0.07	0.005
ADHD	10 (19.2)	12 (20.0)	4 (13.3)	0.49	0.44
Anxiety Disorder	83 (38.1)	118 (42.9)	46 (27.1)	0.02	0.001
Bipolar Disorder	16 (32.7)	26 (40.6)	14 (42.4)	0.37	0.86
Depression	118 (31.7)	147 (35.2)	88 (27.4)	0.22	0.02
Eating Disorder	11 (31.4)	10 (22.7)	5 (11.1)	0.02	0.14
OCD	8 (34.8)	9 (28.1)	4 (28.6)	0.70	0.98
Personality Disorder	1 (11.1)	7 (50.0)	1 (16.6)	1.00	0.32
Schizophrenia	2 (40.0)	6 (85.7)	0 (0.0)	1.00	0.08
Sleep Disorder	25 (22.9)	30 (25.9)	11 (16.2)	0.28	0.13
Self-Injuring Behavior	9 (42.9)	6 (30.0)	4 (19.0)	0.18	0.41
Suicide Attempt	14 (28.6)	20 (33.3)	8 (29.6)	0.92	0.73

ADHD=Attention-deficit/hyperactivity disorder; ASD=Autism spectrum disorder; DD=Developmental disorder; n=Number; OCD=Obsessive-compulsive disorder; POP=Population controls; SSRI=Selective serotonin reuptake inhibitor

[a]Use of antidepressants and diagnoses of psychiatric conditions were independently assessed. The psychiatric condition listed in the table may not be the indication for the mother's SSRI treatment. This table excludes 9 mothers who used SSRIs during pregnancy but did not have a reported/documented psychiatric condition (4 in DD and 5 in POP).

[b]The proportion of women with each specific psychiatric condition who used SSRIs during pregnancy. The denominators for each psychiatric condition are listed in Table 2.

Table 4

Odds of ASD or DD in Offspring Associated with Maternal Psychiatric Conditions and SSRI Use During Pre-conception and/or Pregnancy, Study to Explore Early Development, 2002–2006 and 2008–2011 Births.

	ASD	DD	POP	ASD vs. POP	DD vs. POP
	$n_{exposed}$	nexposed	nexposed	Adj-OR[c] (95% CI)	Adj-OR[c] (95% CI)
All Mothers [a]					
Maternal Psychiatric Condition (Psy Yes vs. Psy No)					
T0	448	550	416	1.61 (1.36 – 1.91)	1.41 (1.21 – 1.65)
T1	293	356	225	1.91 (1.55 – 2.34)	1.65 (1.36 – 2.01)
T2	304	348	218	2.04 (1.66 – 2.50)	1.65 (1.36 – 2.01)
T3	323	368	241	1.95 (1.60 – 2.38)	1.59 (1.32 – 1.92)
PG	348	404	264	1.93 (1.59 – 2.34)	1.60 (1.33 – 1.92)
Maternal Psychiatric Condition and No Maternal SSRI Use (Psy Yes + SSRI No vs. Psy No)					
T0	329	392	328	1.50 (1.25 – 1.81)	1.28 (1.08 – 1.52)
T1	179	212	144	1.78 (1.39 – 2.28)	1.50 (1.19 – 1.90)
T2	190	206	140	1.96 (1.53 – 2.51)	1.47 (1.16 – 1.87)
T3	206	221	160	1.83 (1.45 – 2.32)	1.41 (1.12 – 1.77)
PG	223	248	177	1.81 (1.44 – 2.27)	1.44 (1.15 – 1.79)
Maternal Psychiatric Condition and Maternal SSRI Use (Psy Yes + SSRI Yes vs. Psy No)					
T0	95	137	70	1.98 (1.42 – 2.77)	2.10 (1.54 – 2.85)
T1	86	120	63	1.98 (1.39 – 2.81)	2.06 (1.49 – 2.86)
T2	92	104	64	2.04 (1.45 – 2.89)	1.80 (1.30 – 2.51)
T3	98	109	67	2.18 (1.56 – 3.05)	1.77 (1.28 – 2.45)
PG	115	145	81	2.05 (1.50 – 2.80)	1.92 (1.43 – 2.57)
Restricted to Mothers with Psychiatric Condition [b]					
Maternal SSRI Use (Psy Yes + SSRI Yes vs. Psy Yes + SSRI No)					
T0	95	137	70	1.36 (0.96 – 1.94)	1.69 (1.21 – 2.35)
T1	86	120	63	1.14 (0.76 – 1.72)	1.46 (0.99 – 2.15)
T2	92	104	64	1.06 (0.71 – 1.57)	1.26 (0.85 – 1.87)
T3	98	109	76	1.19 (0.81 – 1.75)	1.32 (0.90 – 1.92)
PG	115	145	81	1.14 (0.80 – 1.62)	1.38 (0.98 – 1.95)

Adj-OR=Adjusted odds ratio; ASD=Autism spectrum disorder; CI=Confidence interval; DD=Developmental disorder; n=Number; OR=Odds ratio; PG=Anytime during pregnancy; POP=Population controls; SSRI=Selective serotonin reuptake inhibitor; T0=3 months before conception; T1=Trimester one; T2=Trimester two;

T3=Trimester three

[a]Reference group only includes children who were unexposed to both maternal psychiatric condition and SSRIs throughout pre-conception and pregnancy (ASD, n=867; DD, n=1157; POP, n=1216).

[b]Reference group only includes children of mothers with an active maternal psychiatric condition during the specific time period and no SSRI exposure throughout pre-conception and pregnancy (ASD, n ranged from 179 to 329; DD, n ranged from 206 to 392; POP, n ranged from 140 to 328). Mothers in the reference group included those who used other forms of psychiatric treatment, including non-SSRI medications and therapy.

[C]Adjusted ORs were adjusted by the following variables: maternal age (continuous), maternal race, maternal education, family income, and smoking history.