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Preschool Outcomes Following Prenatal Serotonin Reuptake Inhibitor Exposure:

Differences in Language and Behavior, but Not Cognitive Function

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ABSTRACT

Objective: To test the hypothesis that prenatal exposure to serotonin reuptake inhibitors (SRIs) is associated with language and behavioral outcomes in preschool-aged children, while accounting for confounds such as concomitant exposures and maternal mental illness.

Method: An observational, prospective, longitudinal study of mental illness in pregnancy was conducted at a university-based women's mental health clinic (April 2010–November 2012). A sample of 178 mother-child dyads participated in a laboratory visit at preschool age (2.5–5.5 years). The majority of women (87%) received psychotropic medication during pregnancy. Psychiatric status (based on *DSM-IV*), other medication use, and substance use were serially assessed and tested as confounds. Primary outcome measures included standardized measures of expressive language and cognitive function and mother and alternate caregiver ratings of child behavior problems, including the Pervasive Developmental Disorders (PDD) subscale of the Child Behavior Checklist.

Results: Linear regression analyses revealed that, after controlling for relevant covariates, expressive language scores from the Test of Early Language Development, 3rd edition, were negatively associated with prenatal SRI exposure ($\beta = -0.15$, $t = -2.41$), while the PDD behavioral problems subscales completed by alternate caregivers and mothers were positively associated with prenatal SRI exposure ($\beta = 0.17$, $t = 2.01$; $\beta = 0.16$, $t = 2.00$, respectively). Cognitive function, measured using the Differential Ability Scales, 2nd edition, was not associated with any medication exposures.

Conclusions: The current data suggest a small but significant association between prenatal SRI exposure and preschool outcomes, including expressive language and behavior problems. These data corroborate data from recent, population-based studies, although overall, published findings are mixed. Replication and identification of moderating risk factors are needed to understand potential clinical implications.

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The recent increase in pharmacologic treatment for mood disorders during pregnancy[1–3] highlights the need for careful scrutiny of outcomes. Common treatment options include selective serotonin reuptake inhibitors (SSRIs) and other drugs such as venlafaxine and clomipramine, collectively referred to as serotonin reuptake inhibitors (SRIs).[1,4] Human research investigating the effects of prenatal SRI exposure on infant and child development has produced mixed results, with several studies reporting negative findings.[5–10] In a recent review,[11] only 2 of 12 included studies reported significant effects of SRI exposure on neurodevelopmental outcomes, and most focused on infants.

A Kaiser Permanente sample[12] noted a 2-fold increase in maternal prenatal SSRI use (and a 4-fold increase in maternal first trimester SSRI use) in children diagnosed with an autism spectrum disorder (ASD) compared to nondiagnosed controls. Dual-action antidepressants were not associated with an increased risk of ASDs, although only 10 women were prescribed those antidepressants, and thus, analyses were quite likely underpowered.[13] Small but significant differences in sample characteristics were noted and statistically controlled for. Two additional recent cohort studies[14,15] also reported links between prenatal antidepressant use and risk of ASDs, while in 2 other large studies,[16,17] the association between antidepressant exposure and ASDs seemed to be driven more by maternal affective disorder than by medication per se. Potentially related, prenatal antidepressant exposure was associated with altered developmental trajectories of infant speech perception, which authors warn may be an indicator of future communication difficulties.[18]

Limitations across the majority of investigations include reliance on maternal reports for perinatal exposures and mostly retrospective tracking of maternal prenatal symptoms, which our group has demonstrated to produce a recall bias resulting in an underreporting of prenatal depression.[19] Further, most of these studies did not compare the potential developmental effects of SRI exposure to those associated with exposure to maternal depressive symptoms. The current study sought to address these gaps in the literature by using a prospectively characterized cohort of mother-child dyads to investigate potential associations between prenatal depressive symptoms, level of exposure to SRIs during gestation, and language and social behavioral outcomes measured in preschool-aged children. Specifically, we attempted to replicate recent findings[12,14,18] that maternal SRI use during pregnancy will increase the risk for language deficits as well as autism spectrum behaviors.

Clinical Points

- A significant number of pregnant women present with depression. Long-term, prospective studies following the children of these women are lacking.
- Study findings do not suggest that physicians avoid serotonin reuptake inhibitor (SRI) treatment for all pregnant women, but instead suggest that more research is needed to determine whether certain offspring are at risk for negative outcomes related to prenatal SRI exposure versus untreated and undertreated maternal depression.

METHOD

Participants

Mother-child dyads (N = 178) were recruited from a larger sample of 229 women enrolled in an observational, prospective, longitudinal study at the Emory Women's Mental Health Program, Atlanta, Georgia, which specializes in treatment of perinatal mental illness. Women were assessed at multiple time points throughout pregnancy with self-report and clinician-administered measures of psychiatric symptoms and health, urine toxicology, thyroid function, and weekly documentation of all exposures in pregnancy (prescription, over-the-counter, and environmental).[20–25] To be recruited for the current study, mothers had to participate in the prospective study above, and their children needed to fall in the specific preschool age range. Women with active substance abuse during pregnancy were excluded, and children with identified congenital malformations or serious medical conditions were also excluded.

Children between 2.5 and 5.5 years of age and their mothers were assessed during a 2.5-hour laboratory visit (April 2010–November 2012). After women provided informed consent, maternal interviews and questionnaires were administered. Child evaluations included a developmental assessment of motor, language, and cognitive functioning. The study was approved by the Emory University Institutional Review Board.

Measures

Prenatal measures of psychiatric illness and mood symptoms. The Structured Clinical Interview for *DSM-IV* Axis I Disorders–Patient edition (SCID-I/P)[26] is a widely validated semistructured research interview with strong psychometric properties used to assess current and lifetime history of *DSM-IV* Axis I disorders.[27] The SCID-I/P was administered by a trained research interviewer at enrollment. At each subsequent prenatal visit, the mood modules from the SCID-I/P were administered. The number of visits in which a woman met criteria for mood episode divided by the number of times she was assessed in pregnancy was used as a covariate in the current analyses, reflecting the degree to which the mother experienced mood episodes (accounting for her frequency of visits). The Global Assessment of Functioning (GAF), which reflects the clinician's rating of the patient's worst level of functioning in the month prior to assessment, was recorded at each visit. The Beck Depression Inventory (BDI),[28] a self-report measure of depressive symptoms, was administered at each visit. For women with at least 3 prenatal visits, area-under-the-curve measures were calculated for GAF and BDI scores.

Use of psychotropic medications, in addition to alcohol, tobacco, and caffeine, was assessed with a detailed weekly tracking sheet completed by a study physician. Medications were grouped by class: antidepressants-SRIs (eg, citalopram, fluoxetine, sertraline, venlafaxine); antidepressants-bupropion; mood stabilizers, including antiepileptics (eg, lamotrigine, carbamazepine); atypical antipsychotics (eg, risperidone, quetiapine, olanzapine); anxiolytics (eg, alprazolam, lorazepam, diazepam); and hypnotics (eg, zolpidem, trazodone, diphenhydramine). Women's medication regimen with respect to dosage, timing, and number of medications was adjusted based on clinical symptoms and tolerability. Medication exposure was estimated by multiplying the number of medications within a given class by the number of weeks taken during pregnancy. The primary predictor in the current study was SRI drug weeks (ie, number of SRI medications × number of weeks taken, standardized to 40 weeks gestation). Drug weeks of exposure to other medication classes were tested as potential confounds using the same approach (number of drugs in a given class × number of weeks exposed, standardized to 40 weeks of gestation).[29]

Child measures. Standardized tests and caregiver report measures were administered. The Expressive Language subtest of the Test of Early Language Development, 3rd edition (TELD-3),[30] assesses the child's ability to provide personal information, answer open-ended questions, and use age-appropriate expressive language skills including grammar, syntax, and vocabulary. The TELD-3 can be administered to children aged 2 years 0 months to 7 years 11 months. The Differential Ability Scales, 2nd edition (DAS-II),[31] is a normalized measure of current cognitive functioning administered to children aged 2 years 6 months to 17 years 11 months. The TELD-3 and DAS-II were administered by graduate students blinded to maternal medication and psychiatric status.

The Child Behavior Checklist (CBCL)[32] measures the frequency of common behavior problems in children aged 1.5 to 5 years. The Pervasive Developmental Disorder (PDD) subscale includes 13 items assessing behaviors such as being afraid of new things, avoiding eye contact, not getting along with others, speech problems, and having difficulty when things are out of order. Subscale scores are given as T scores with a mean of 50 and an SD of 10; scores above 65 are considered "at risk." Although the CBCL is not used as a diagnostic tool, children scoring high on the PDD subscale are more likely to evidence behaviors commonly associated with ASDs. The child's mother and an alternate caregiver (eg, father, babysitter, teacher, grandmother) completed the CBCL; 140 of 178 (79%) of the alternate caregiver CBCLs were returned.

Maternal measures. At the preschool follow-up, SCIDs were administered by 1 clinical psychologist and 3 doctoral students. Interrater reliability based on 15% of the sample was adequate for the most common diagnoses (κ values, 0.80–1.00).

Potential confounds. Sociodemographic variables assessed at the preschool follow-up included mother's age and child's age, child's gender, mother's highest level of education, mother's marital status, the number of adults and children living in the home, whether the mother worked outside of the home and the average number of hours worked per week, and whether the child attended a structured early learning program (eg, daycare, preschool). Area-under-the-curve measures were derived for the following prenatal exposures: alcohol, illicit drugs (marijuana), tobacco, and caffeine and for additional psychotropic medication classes: bupropion; mood-stabilizers, including antiepileptics and atypical antipsychotics; anxiolytics; and hypnotics. A child's postpartum psychotropic medication exposure via lactation was coded as a binary (yes/no) variable, collected during postpartum follow-up visits from 0 to 6 months. Labor and delivery records for all mother-child dyads were obtained and extracted to yield the following variables: birth weight, head circumference, estimated gestational age at delivery, delivery method (vaginal vs cesarean delivery), Apgar scores at 1 and 5 minutes, number of delivery complications, and number of pregnancy complications. The prenatal measures of depressive symptoms, mood episodes, and global functioning (described in the Measures section), as well as maternal epileptic status, were also tested as potential confounds.

Statistical Analyses

The primary predictor in the current study was SRI drug weeks. Dependent measures were the (1) Expressive Language standard score from the TELD-3, (2) overall cognitive functioning composite from the DAS-II, (3) PDD subscale completed by mothers, and (4) PDD subscale completed by alternate caregivers. The potential confounds were tested using Pearson correlations, *t* tests, and χ^2 tests. Hierarchical linear regression was used to evaluate the study hypotheses that prenatal SRI exposure would be associated with increased PDD subscale scores and decreased TELD-3 scores. A separate regression model was used for each dependent variable; covariates that were significantly related to that dependent variable were included in block 1 of the regression model, the predictor SRI drug weeks was included in step 2 of the model. Post hoc analyses used logistic regression, partial correlations, and analysis of covariance to further evaluate significant associations. Generalized linear mixed models were incorporated to account for potential effects of 18 sibling pairs in the data.

The PDD subscales completed by both raters were skewed and, thus, log transformed for all analyses. DAS Cognitive and TELD-3 Expressive Language scores were normally distributed.

RESULTS

Sample Characteristics

The sample of women who participated in the preschool follow-up study showed no differences from those who passively or actively refused participation (n = 51) with respect to age at pregnancy ($t_{1,227} = 0.17$, $P = .86$), highest level of education attained ($t_{1,227} = -0.65$, $P = .52$), gestational age of the target child at birth ($t_{1,227} = -0.96$, $P = .34$), or method of delivery (ie, vaginal vs cesarean delivery; $\chi^2_{3,229} = 5.09$, $P = .17$).

Mothers participating in the preschool follow-up study had a mean age of 37.2 years (SD = 4.7). Their median education level was college graduate, and approximately 61% of the mothers worked outside of the home (number of hours ranged from 2 to 70; mean = 20.0 hours, SD = 19.6). Approximately 84% of the women were married or cohabitating with a partner, and another 8% of the sample lived with another adult (eg, parent); thus, about 8% of the sample resided in a single-adult household. Most of the women received psychotropic medication at some point during pregnancy (n = 155; 87%), and 93% of women (n = 165) had a lifetime history of at least 1 Axis I disorder. At the preschool visit, BDI scores ranged from 0 to 53 (mean = 6.9, SD = 8.3). Children participating in the current study ranged in age from 30 to 65 months (mean = 45.2 months, SD = 11.2), and 51.7% were males.

Table 1 compares sample characteristics between SRI-exposed and unexposed children and describes the type of SRI exposures for the sample. Table 2 describes statistically significant associations between potential covariates and primary outcomes of interest. Of note, other psychotropic exposures (bupropion, mood stabilizers, anxiolytics, and hypnotics) were not significantly associated with outcome variables.

Expressive Language and Cognitive Functioning

Linear regression analyses revealed a negative association between SRI drug weeks and TELD-3 Expressive Language scores (Table 2). To assess magnitude of the effect, mean Expressive Language scores were compared between those children prenatally exposed to SRI medications and those unexposed. After controlling for significant confounds, analysis of covariance revealed a modest mean difference of approximately 5 points in Expressive Language scores ($F_{1,144} = 8.594$, $P = .004$). Prenatal SRI exposure was not associated with the DAS-II composite measure of cognitive functioning ($r = 0.016$, $P = .833$, n = 175).

Pervasive Development Disorder Subscale Ratings

Linear regression analyses revealed a positive association between SRI drug weeks and PDD subscale completed by the alternate caregiver (Table 3). Consistently, prenatal SRI exposure was also positively associated with the PDD subscale completed by the mother (Table 4). PDD subscales scores rated by the mother and alternate caregiver were modestly correlated ($r = 0.29$, $P < .001$, n = 142).

Table 1. Description of Sample by Exposure Group

	Assessed in Current Study (N = 178)	Not Exposed to SRIs (n = 76)	Exposed to SRIs (n = 102)
Child age, mean (SD), mo	45.2 (11.2)	45.1 (12.1)	45.2 (10.4)
Child gender, % male	52	55	49
Prenatal BDI score,[a] mean (SD)	10.0 (7.9)	8.3 (6.3)	11.3 (8.8)
Preschool BDI score,[a] mean (SD)	6.9 (8.3)	5.0 (5.2)	8.3 (9.8)
Prenatal BDI < 15, n (%)	88 (54.0)	45 (67.2)	43 (44.8)
SRI exposure type,[b] n			
Citalopram			15
Escitalopram			14
Fluoxetine			21
Paroxetine			7
Sertraline			26
Desvenlafaxine			1
Duloxetine			2
Venlafaxine			20

[a]Denotes statistical difference between groups, $P < .05$.
[b]Other antidepressant exposures: bupropion = 27, mirtazapine = 3; some women were exposed to multiple antidepressants.
Abbreviations: BDI = Beck Depression Inventory, SRI = serotonin reuptake inhibitor.

Table 2. Multiple Linear Regression Results for TELD-3[a,b]

Independent Variable	β	Unstandardized B Coefficient	95% CI for B	*P* Value
Maternal education[c]	0.118	1.187	−0.025 to 2.398	.055
Prenatal BDI AUC	0.023	0.001	−0.007 to 0.009	.818
Prenatal mood episodes	−0.083	−5.332	−17.590 to 6.926	.391
Prenatal caffeine	−0.043	−0.003	−0.011 to 0.005	.480
Prenatal alcohol	−0.029	−0.018	−0.103 to 0.068	.678
Prenatal tobacco	0.038	0.001	−0.003 to 0.006	.604
Gestational age at delivery	0.089	0.887	−0.308 to 2.081	.144
Apgar at 5 minutes	0.059	1.783	−1.792 to 5.357	.326
Child age (months)	−0.509	−0.693	−0.862 to −0.525	< .001
DAS-II (cognitive ability)	0.556	0.550	0.422 to 0.679	< .001
Prenatal SRI (drug weeks)	**−0.146**	**−0.105**	**−0.190 to −0.019**	**.017**

[a]TELD-3 score: mean = 100, SD = 15. Bolded values show significance at $P < .05$, $t = -2.41$.
[b]The following variables were tested as covariates and were not significantly associated with the TELD: mother's age; child's gender; mother's marital status; the number of adults and children living in the home; mother's work status; average number of hours mother worked per week; whether the child attended a structured early learning program; maternal depressive symptoms (BDI) at preschool visit; area under the curve measures for prenatal exposure to marijuana, bupropion, mood stabilizers, anxiolytics, and hypnotics; postpartum exposure to SRIs, bupropion, mood stabilizers, anxiolytics, and hypnotics; birth weight; head circumference; delivery method; number of delivery complications; number of pregnancy complications; maternal prenatal global assessment of functioning scores; and maternal epileptic status.
[c]Maternal education was measured on an 6-point scale ranging from < 8th grade to completing graduate degree.
Abbreviations: AUC = area under the curve; BDI = Beck Depression Inventory; DAS-II = Differential Ability Scales, 2nd edition; SRI = serotonin reuptake inhibitor; TELD-3 = Test of Early Language Development, 3rd edition.

To facilitate interpretation of these effects, cutoff scores ($T > 65$) were used in logistic regression models to test whether the SRI drug weeks variable was associated with increased likelihood of clinically elevated PDD subscales. In clinical practice, scores above 65 are considered "at risk." For mother-rated CBCLs, PDD scores for 15 children fell above the cutoff, and children with prenatal SRI exposure were statistically more likely to score in the PDD at-risk range (OR = 1.05; 95% CI, 1.01 to 1.08; $P < .02$). However, prenatal SRI exposure was not associated with increased risk of elevated PDD scores rated by alternate caregivers (OR = 1.01; 95% CI, 0.98 to 1.05; $P = .52$); 10 children fell in the at-risk range as rated by alternate caregivers.

Post Hoc Analyses

To examine whether nonindependence of siblings (n = 18 pairs) biased our results, generalized linear mixed models analogous to the linear regression models described above were run. This technique yielded a nested model with sibling pairs nested within families. Significant results held for associations between prenatal SRI exposure and Expressive Language scores, mother-rated PDD behaviors, and alternate caregiver–rated PDD behaviors (data not shown). In addition, 10 women were diagnosed with a psychotic disorder (eg, schizophrenia, schizoaffective disorder). Given that a family history of a psychotic disorder may act as an independent risk factor for ASDs[33] and, therefore, elevated PDD behaviors, we removed these mother-child dyads from the sample and reexecuted the regression models. Results were mostly unchanged: Expressive Language ($\beta = -0.143$, $t = -2.320$, $P = .022$, $\Delta R^2 = 0.019$), mother-rated PDD behavior ($\beta = 0.160$, $t = 1.927$, $P = .05$, $\Delta R^2 = 0.021$), and alternate caregiver-rated PDD behavior ($\beta = 0.179$, $t = 2.077$, $P = .040$, $\Delta R^2 = 0.031$).

DISCUSSION

The prospective nature of our collected data supported our efforts to delineate associations between SRI exposure in pregnancy and longer-term outcomes in offspring. Population-based studies recently linked prenatal SSRI exposure to an increased risk for ASDs,[12,14,15] although at least 2 large studies[16,17] reported negative findings once maternal mental illness was accounted for. While the current study did not assess for diagnoses of ASDs per se, measures of expressive language and behavior problems linked to ASD were assessed using clinician, mother, and alternate caregiver ratings. Several observational studies have failed to find associations between prenatal SRI exposure and neurodevelopmental outcomes using clinical assessment,[7,9] standardized measures,[6,8,34] and physician examinations.[10] Methodological issues may have contributed to the discordant results. Of note, the number of medication-exposed infants in most previous studies is fewer than 50, the inclusion of prenatal and postnatal maternal symptoms is rare, and many studies did not use standardized developmental measures. The 1 research group to prospectively examine expressive language outcomes in children prenatally exposed to antidepressants compared to unexposed controls showed no group differences,[5,35] but language measures were associated with postpartum depression. Differences in statistical approach, outcome measures, and included covariates may have accounted for the discrepant findings. Given the mixed findings, replication is clearly needed.

Table 3. Multiple Linear Regression Results for Alternate Caregiver–Rated PDD[a,b]

Independent Variable	β	Unstandardized B Coefficient	95% CI for B	*P* Value
Maternal epilepsy	−0.044	−0.028	−0.134 to 0.078	.607
No. of children in the home	−0.124	−0.015	−0.036 to 0.005	.146
Prenatal SRI (drug weeks)	**0.171**	**0.001**	**< 0.001 to 0.002**	**.047**

[a]PDD subscale score reflects a *T* score with a mean of 50 and an SD of 10. Bolded values show significance at $P < .05$, $t = 2.01$.

[b]The following variables were tested as covariates and were not significantly associated with the PDD subscale: child's age; child's gender; mother's age; mother's marital status; number of adults in the home; mother's work status; average hours mother worked per week; whether the child attended a structured early learning program; maternal depressive symptoms (BDI) at preschool visit; area under the curve measures for prenatal exposure to marijuana, alcohol, caffeine, tobacco, bupropion, mood stabilizers, anxiolytics, and hypnotics; postpartum exposure to SRIs, bupropion, mood stabilizers, anxiolytics, and hypnotics; birth weight, Apgar scores; gestational age; head circumference; delivery method; number of delivery complications; number of pregnancy complications; and maternal prenatal measures of depressive symptoms, mood episodes, and global assessment of functioning.

Abbreviations: PDD = Pervasive Developmental Disorder subscale of the Child Behavior Checklist, SRI = serotonin reuptake inhibitor.

Table 4. Multiple Linear Regression Results for Mother-Rated PDD Scores[a,b]

Independent Variable	β	Unstandardized B Coefficient	95% CI for B	*P* Value
Preschool BDI	0.036	< 0.001	−0.002 to 0.002	.646
Postpartum antidepressant (yes/no)	0.124	0.027	−0.008 to 0.061	.131
Prenatal tobacco	0.243	< 0.001	< 0.001 to < 0.001	.002
Prenatal SRI (drug weeks)	**0.163**	**0.001**	**< 0.001 to 0.002**	**.048**

[a]PDD subscale score reflects a *T* score with a mean of 50 and an SD of 10. Bolded values show significance at $P < .05$, $t = 2.00$.

[b]The following variables were tested as covariates and were not significantly associated with the PDD: child's age; child's gender; mother's age; mother's marital status; number of adults and children living in the home; mother's work status; average hours mother worked per week; whether the child attended a structured early learning program; maternal depressive symptoms (BDI) at preschool visit; area under the curve measures for prenatal exposure to marijuana, alcohol, caffeine, bupropion, mood stabilizers, anxiolytics, and hypnotics; postpartum exposure to bupropion, mood stabilizers, anxiolytics, and hypnotics; birth weight; head circumference; Apgar scores; gestational age; delivery method; number of delivery complications; number of pregnancy complications; maternal prenatal measures of depressive symptoms, mood episodes, global assessment of functioning; and maternal epileptic status.

Abbreviations: BDI = Beck Depression Inventory, PDD = Pervasive Developmental Disorder subscale of the Child Behavior Checklist, SRI = serotonin reuptake inhibitor.

Effect sizes in the current study are consistent with the heterogeneous nature of complex disorders such as ASDs, for which multiple etiologic factors are likely at play. Likewise, only a proportion of the children who were exposed prenatally to SRIs showed altered language or behavioral outcomes. Future studies should focus on moderating factors that help to explain the variability in exposure effects, including genetic variation.[36–38] Prenatal exposure to SRIs very likely impacts a subset of offspring; thus, identifying moderators, such as genetic markers, is a critical next step. Identifying maternal physiological factors that influence the extent of fetal medication exposure[39] may also be relevant.

The fact that no other psychotropic medication classes (eg, anxiolytics, antipsychotics) were associated with ASD-related behaviors or any other child outcomes should also be highlighted. In addition, prenatal SRI exposure was related to language and PDD subscale scores but not to general cognitive functioning. The study by Rai et al[14] found prenatal antidepressant exposure to be associated with increased risk of ASD without intellectual impairment but not increased risk of ASD with intellectual impairment. The children without intellectual impairment reflect a specific subset of the ASD continuum and include those with Asperger syndrome and specific deficits in social communication. Future studies should focus on identifying neural mechanisms that may link prenatal SRI exposure to specific deficits observed in ASDs; including measures of pragmatic language and social communication in follow-up studies would be particularly helpful. A recent, large study using health records found an association between prenatal SRI exposure and attention-deficit/hyperactivity disorder (ADHD) but not ASDs, after controlling for maternal psychiatric illness variables.[17] The current study, on the other hand, found an association with only the PDD subscale and not the ADHD subscale of the CBCL, a 100-item behavior checklist. The study by Clements et al[17] examined older children and used medical record diagnoses rather than symptom checklists, which could have accounted for the discrepant findings. Given the small sample size of the current study, we cannot rule out the possibility of an undetected association with ADHD symptoms, and this further indicates a need for replication, particularly in studies using sensitive measures of neurobehavioral functioning.

Despite the detailed information available and thorough statistical interrogation of the data, it is not possible to assign a causal relationship between SRI exposure and risk for ASDs. Due to the ethical limitations of randomly assigning women to treatment conditions, this study is by nature, observational. Thus, the type of medication, dosages, and timing vary for each individual, as do the patients' diagnostic histories. Using a multimethod approach including clinician-administered and self-report measures helped to capture this inherent variability. While the observational study design limits our ability to draw causal inferences, our sample closely matches the day-to-day clinical scenarios faced by treating physicians.

The issue of determining the ideal control group remains a potentially contentious debate. As noted, our sample had a limited group of nonexposed infants and non-ill mothers. The significant associations with covariates underscore the potential mediating factors that are often associated with greater maternal psychopathology (eg, tobacco use). Another point of debate includes the accurate grouping of medications into classes. Grouping medications is necessary given that most studies, including population-based studies, lack sufficient statistical power to measure the effects of

individual medication exposures. We used an a priori approach, as medications were grouped prior to all analyses, based on a series of discussions by study psychiatrists and other investigators. Reasonable alternatives to our groupings could certainly be proposed, and which medications were and were not included may contribute to discrepant results in the literature.

Left untreated, maternal prenatal mood disorders are associated with many adverse neurodevelopmental and behavioral outcomes in children, including lower activity levels, decreased motor tone, altered stress regulation, brain morphology differences, increased irritability, negative affectivity, and childhood behavior problems.[40–49] Given that both psychiatric illness and its treatment may negatively impact offspring, and that both have independently been associated with ASD risk, patients and providers have to be cautious in terms of discontinuing or avoiding medication use in pregnancy. Discontinuation of medication during pregnancy is associated with a significantly higher rate of relapse for major depressive disorder: 68% compared to 24% of women who continue medication.[50]

Although many studies[51–54] suggest the ASDs evidence high heritability, approximately 55% of variance in ASD risk is attributable to environmental factors.[55] Thus, identifying environmentally mediating risk factors of ASDs is paramount to prevention. The current data, while speculative, suggest a small but significant association between prenatal SRI exposure and outcomes typically associated with ASDs, including mild expressive language deficits. While the direct clinical import of these findings is limited pending replication, our data suggest that a subset of children may be vulnerable to the effects of prenatal SRI exposure. Replication with samples that include important comparator groups and identification of moderating risk factors is critical for understanding the clinical implications of these findings. Future studies would benefit from efforts to combine data sets across multiple clinical sites, given the relatively low incidence of prenatal exposure and the modest prevalence rate of ASDs. Whether the current findings reflect a delay or a deficit is currently unknown, and prospective longitudinal data across childhood and adolescence would be needed to test those hypotheses. These novel prospective data indicating an association between SRI exposure and ASD must be balanced with the adverse effects of maternal depression in the clinical decision process. Similarly, these data provide a foundation for future clinical and laboratory investigations in advancing our understanding of the etiopathogenesis of ASDs.

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Drug names: alprazolam (Xanax, Niravam, and others), bupropion (Wellbutrin and others), carbamazepine (Tegretol, Epitol, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desvenlafaxine (Pristiq, Khedezla, and others), diazepam (Valium and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), lamotrigine (Lamictal and others), lorazepam (Ativan and others), mirtazapine (Remeron and others), olanzapine (Zyprexa and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), sertraline (Zoloft and others), zolpidem (Ambien, Edluar, and others).

Author contributions: Drs Johnson and Brennan take responsibility for the integrity of the work in the current study, from inception to submitted manuscript. Drs Smith, Stowe, and Newport made substantial contributions to study design, acquisition and interpretation of data, and drafting and revising the manuscript. Drs Smith and Brennan were principal investigators on the primary grant(s) supporting the current study.

Potential conflicts of interest: During his career, **Dr Newport** has received research support from Eli Lilly, GlaxoSmithKline, Janssen, the National Alliance for Research on Schizophrenia and Depression (NARSAD), the National Institutes of Health (NIH), and Wyeth; has served on speaker bureaus and/or received honoraria from AstraZeneca, Eli Lilly, GlaxoSmithKline, Pfizer, and Wyeth; and has served on advisory boards for GlaxoSmithKline. **Dr Stowe** (lifetime) has received research support from the NIH, GlaxoSmithKline, Pfizer, and Wyeth; has served on speaker and/or advisory boards for Pfizer, Eli Lilly, Wyeth, Bristol-Myers Squibb, and GlaxoSmithKline; has served as a consultant for Bristol-Myers Squibb and Wyeth; and has received honoraria from Eli Lilly, Forest, GlaxoSmithKline, Pfizer, and Wyeth. **Drs Brennan**, **Johnson**, and **Smith** have no conflicts to report.

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REFERENCES

1. Cooper WO, Willy ME, Pont SJ, et al. Increasing use of antidepressants in pregnancy. *Am J Obstet Gynecol*. 2007;196(6):544e1–544e5.
2. Alwan S, Reefhuis J, Rasmussen SA, et al; National Birth Defects Prevention Study. Patterns of antidepressant medication use among pregnant women in a United States population. *J Clin Pharmacol*. 2011;51(2):264–270.
3. Bakker MK, Kölling P, van den Berg PB, et al. Increase in use of selective serotonin reuptake inhibitors in pregnancy during the last decade, a population-based cohort study from the Netherlands. *Br J Clin Pharmacol*. 2008;65(4):600–606.
4. Andrade SE, Raebel MA, Brown J, et al. Use of antidepressant medications during pregnancy: a multisite study. *Am J Obstet Gynecol*. 2008;198(2):194e1–194e5.
5. Nulman I, Rovet J, Stewart DE, et al. Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. *Am J Psychiatry*. 2002;159(11):1889–1895.
6. Oberlander TF, Misri S, Fitzgerald CE, et al. Pharmacologic factors associated with transient neonatal symptoms following prenatal psychotropic medication exposure. *J Clin Psychiatry*. 2004;65(2):230–237.
7. Heikkinen T, Ekblad U, Palo P, et al. Pharmacokinetics of fluoxetine and norfluoxetine in pregnancy and lactation. *Clin Pharmacol Ther*. 2003;73(4):330–337.
8. Reebye PN, Morison SJ, Panikkar H, et al. Affect expression in prenatally psychotropic exposed and nonexposed mother–infant dyads. *Infant Ment Health J*. 2002;23(4):403–416.
9. Heikkine T, Ekblad U, Laine K. Transplacental transfer of citalopram, fluoxetine and their primary demethylated metabolites in isolated perfused human placenta. *BJOG*. 2002;109(9):1003–1008.
10. Simon GE, Cunningham ML, Davis RL. Outcomes of prenatal antidepressant exposure. *Am J Psychiatry*. 2002;159(12):2055–2061.
11. Gentile S, Galbally M. Prenatal exposure to antidepressant medications and neurodevelopmental outcomes: a systematic review. *J Affect Disord*. 2011;128(1–2):1–9.
12. Croen LA, Grether JK, Yoshida CK, et al. Antidepressant use during pregnancy and childhood autism spectrum disorders. *Arch Gen Psychiatry*. 2011;68(11):1104–1112.
13. Andrade C. Antidepressant use in pregnancy and risk of autism spectrum disorders: a critical examination of the evidence. *J Clin Psychiatry*. 2013;74(9):940–941.
14. Rai D, Lee BK, Dalman C, et al. Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. *BMJ*. 2013;346:f2059.
15. Harrington RA, Lee L-C, Crum RM, et al. Prenatal SSRI use and offspring with autism spectrum disorder or developmental delay. *Pediatrics*. 2014;133(5):e1241–e1248.
16. Sørensen MJ, Grønborg TK, Christensen J, et al.

Antidepressant exposure in pregnancy and risk of autism spectrum disorders. *Clin Epidemiol*. 2013;5:449–459.

17. Clements CC, Castro VM, Blumenthal SR, et al. Prenatal antidepressant exposure is associated with risk for attention-deficit hyperactivity disorder but not autism spectrum disorder in a large health system. *Mol Psychiatry*. 2015;20(6):727–734.
18. Weikum WM, Oberlander TF, Hensch TK, et al. Prenatal exposure to antidepressants and depressed maternal mood alter trajectory of infant speech perception. *Proc Natl Acad Sci U S A*. 2012;109(suppl 2):17221–17227.
19. Newport DJ, Brennan PA, Green P, et al. Maternal depression and medication exposure during pregnancy: comparison of maternal retrospective recall to prospective documentation. *BJOG*. 2008;115(6):681–688.
20. Smith AK, Newport DJ, Ashe MP, et al. Predictors of neonatal hypothalamic-pituitary-adrenal axis activity at delivery. *Clin Endocrinol (Oxf)*. 2011;75(1):90–95.
21. Newport DJ, Ji S, Long Q, et al. Maternal depression and anxiety differentially impact fetal exposures during pregnancy. *J Clin Psychiatry*. 2012;73(2):247–251.
22. Johnson KC, LaPrairie JL, Brennan PA, et al. Prenatal antipsychotic exposure and neuromotor performance during infancy. *Arch Gen Psychiatry*. 2012;69(8):787–794.
23. Newport DJ, Ritchie JC, Knight BT, et al. Venlafaxine in human breast milk and nursing infant plasma: determination of exposure. *J Clin Psychiatry*. 2009;70(9):1304–1310.
24. Juric S, Newport DJ, Ritchie JC, et al. Zolpidem (Ambien) in pregnancy: placental passage and outcome. *Arch Women Ment Health*. 2009;12(6):441–446.
25. Pennell PB, Peng L, Newport DJ, et al. Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. *Neurology*. 2008;70(22 pt 2):2130–2136.
26. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV Axis I Disorders–Patient Edition (SCID-I/P, Version 2.0)*. New York, NY: Biometrics Research Department, New York State Psychiatric Institute; 2002.
27. Lobbestael J, Leurgans M, Arntz A. Inter-rater reliability of the Structured Clinical Interview for *DSM-IV* Axis I Disorders (*SCID I*) and Axis II Disorders (*SCID II*). *Clin Psychol Psychother*. 2011;18(1):75–79.
28. Beck AT, Steer RA, Brown GK. *The Beck Depression Inventory*. 2nd ed. San Antonio, TX: The Psychological Corporation; 1996.
29. Smith AK, Conneely KN, Newport DJ, et al. Prenatal antiepileptic exposure associates with neonatal DNA methylation differences. *Epigenetics*. 2012;7(5):458–463.
30. Hresko WP, Reid DK, Hammill DD. *TELD-3: Test of Early Language Development: Examiner's Manual*. Austin, TX: Pro-Ed, Inc; 1999.
31. Elliot CD. *Differential Ability Scales, Second Edition: Examiner's Manual*. San Antonio, TX: Harcourt Assessment; 2007.
32. Achenbach TM, Rescorla LA. *Manual for the ASEBA Preschool Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families; 2000.
33. Jokiranta E, Brown AS, Heinimaa M, et al. Parental psychiatric disorders and autism spectrum disorders. *Psychiatry Res*. 2013;207(3):203–211.
34. Morrison JL, Riggs KW, Chien C, et al. Chronic maternal fluoxetine infusion in pregnant sheep: effects on the maternal and fetal hypothalamic-pituitary-adrenal axes. *Pediatr Res*. 2004;56(1):40–46.
35. Nulman I, Rovet J, Stewart DE, et al. Neurodevelopment of children exposed in utero to antidepressant drugs. *N Engl J Med*. 1997;336(4):258–262.
36. Weikum WM, Brain U, Chau CM, et al. Prenatal serotonin reuptake inhibitor (SRI) antidepressant exposure and serotonin transporter promoter genotype (SLC6A4) influence executive functions at 6 years of age. *Front Cell Neurosci*. 2013;7:180.
37. Hilli J, Heikkinen T, Rontu R, et al. MAO-A and COMT genotypes as possible regulators of perinatal serotonergic symptoms after in utero exposure to SSRIs. *Eur Neuropsychopharmacol*. 2009;19(5):363–370.
38. Oberlander TF, Bonaguro RJ, Misri S, et al. Infant serotonin transporter (SLC6A4) promoter genotype is associated with adverse neonatal outcomes after prenatal exposure to serotonin reuptake inhibitor medications. *Mol Psychiatry*. 2008;13(1):65–73.
39. DeVane CL, Stowe ZN, Donovan JL, et al. Therapeutic drug monitoring of psychoactive drugs during pregnancy in the genomic era: challenges and opportunities. *J Psychopharmacol*. 2006;20(4 suppl):54–59.
40. Brand SR, Brennan PA. Impact of antenatal and postpartum maternal mental illness: how are the children? *Clin Obstet Gynecol*. 2009;52(3):441–455.
41. Bonari L, Pinto N, Ahn E, et al. Perinatal risks of untreated depression during pregnancy. *Can J Psychiatry*. 2004;49(11):726–735.
42. Davalos DB, Yadon CA, Tregellas HC. Untreated prenatal maternal depression and the potential risks to offspring: a review. *Arch Women Ment Health*. 2012;15(1):1–14.
43. Diego MA, Field T, Hernandez-Reif M. Prepartum, postpartum and chronic depression effects on neonatal behavior. *Infant Behav Dev*. 2005;28(2):155–164.
44. Diego MA, Field T, Hernandez-Reif M, et al. Prepartum, postpartum, and chronic depression effects on newborns. *Psychiatry*. 2004;67(1):63–80.
45. Goodman SH, Gotlib IH. Risk for psychopathology in the children of depressed mothers: a developmental model for understanding mechanisms of transmission. *Psychol Rev*. 1999;106(3):458–490.
46. O'Donnell KJ, Glover V, Jenkins J, et al. Prenatal maternal mood is associated with altered diurnal cortisol in adolescence. *Psychoneuroendocrinology*. 2013;38(9):1630–1638.
47. Sohr-Preston SL, Scaramella LV. Implications of timing of maternal depressive symptoms for early cognitive and language development. *Clin Child Fam Psychol Rev*. 2006;9(1):65–83.
48. Field T. Infants of depressed mothers. *Infant Behav Dev*. 1995;18(1):1–13.
49. Rifkin-Graboi A, Bai J, Chen H, et al. Prenatal maternal depression associates with microstructure of right amygdala in neonates at birth. *Biol Psychiatry*. 2013;74(11):837–844.
50. Cohen LS, Altshuler LL, Harlow BL, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA*. 2006;295(5):499–507.
51. Folstein S, Rutter M. Infantile autism: a genetic study of 21 twin pairs. *J Child Psychol Psychiatry*. 1977;18(4):297–321.
52. Steffenburg S, Gillberg C, Hellgren L, et al. A twin study of autism in Denmark, Finland, Iceland, Norway and Sweden. *J Child Psychol Psychiatry*. 1989;30(3):405–416.
53. Bailey A, Le Couteur A, Gottesman I, et al. Autism as a strongly genetic disorder: evidence from a British twin study. *Psychol Med*. 1995;25(1):63–77.
54. Lichtenstein P, Carlström E, Råstam M, et al. The genetics of autism spectrum disorders and related neuropsychiatric disorders in childhood. *Am J Psychiatry*. 2010;167(11):1357–1363.
55. Hallmayer J, Cleveland S, Torres A, et al. Genetic heritability and shared environmental factors among twin pairs with autism. *Arch Gen Psychiatry*. 2011;68(11):1095–1102.