Archival Report

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Prenatal Selective Serotonin Reuptake Inhibitor Exposure, Depression, and Brain Morphology in Middle Childhood: Results From the ABCD Study

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ABSTRACT

BACKGROUND: Prenatal selective serotonin reuptake inhibitor (SSRI) exposure has been inconsistently linked to depression, and little is known about neural correlates. We examined whether prenatal SSRI exposure is associated with depressive symptoms and brain structure during middle childhood.

METHODS: Prenatal SSRI exposure (retrospective caregiver report), depressive symptoms (caregiver-reported Child Behavior Checklist), and brain structure (magnetic resonance imaging–derived subcortical volume; cortical thickness and surface area) were assessed in children (analytic *n*s = 5420–7528; 235 with prenatal SSRI exposure; 9–10 years of age) who completed the baseline Adolescent Brain Cognitive Development Study session. Linear mixed-effects models nested data. Covariates included familial, pregnancy, and child variables. Matrix spectral decomposition adjusted for multiple testing.

RESULTS: Prenatal SSRI exposure was not independently associated with depression after accounting for recent maternal depressive symptoms. Prenatal SSRI exposure was associated with greater left superior parietal surface area (b = 145.3 mm^2, p = .00038) and lateral occipital cortical thickness (b = 0.0272 mm, p = .0000079); neither was associated with child depressive symptoms. Child depression was associated with smaller global brain structure.

CONCLUSIONS: Our findings, combined with adverse outcomes of exposure to maternal depression and the utility of SSRIs for treating depression, suggest that risk for depression during middle childhood should not discourage SSRI use during pregnancy. Associations between prenatal SSRI exposure and brain structure were small in magnitude and not associated with depression. It will be important for future work to examine associations between prenatal SSRI exposure and depression through young adulthood, when risk for depression increases.

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Following the release of Prozac (Eli Lilly and Co.), the first selective serotonin reuptake inhibitor (SSRI), to the United States market in 1988, antidepressant use increased by nearly 600% (from 1.8% to 10.7% of American adults) (1). As women are more likely to suffer from depression than men and the period of greatest risk occurs during reproductive years (2), it is perhaps unsurprising that among the 50% of pregnant women taking prescribed medication, SSRIs are one of the most commonly used (3,4). However, the potential impact of prenatal SSRI exposure is poorly understood.

There is mixed evidence that prenatal SSRI exposure may be associated with adverse physical (e.g., diminished fetal growth, hypertension) (5,6) and mental health outcomes (7). For child depression (Table 1), larger studies have generally identified associations between prenatal SSRI exposure and depression-related outcomes (8–12), while the majority of null associations have arisen from relatively smaller samples (13–17). It remains unclear to what extent lifetime maternal depression, maternal depression during pregnancy, or maternal depression during childhood may potentially confound observed associations (Table 1).

Contrasting a relatively sizable literature investigating prenatal SSRI exposure and depression-related outcomes in young children, there has been limited investigation of putative neural mechanisms through which risk may arise. Indeed, we are aware of only two magnetic resonance imaging (MRI)

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Table 1. Summary of Existing Relevant Literature

Study	Sample	Controlled for Maternal Depression?	Relevant Findings
Studies Reporting That Prenatal SSRI Exposure Is Associated With Internalizing Symptoms			
Hanley *et al.* (38)	Prenatal SRI–exposed (n = 44) and –unexposed (n = 66) 3- to 6-year-old children	Yes (HDRS or BDI during pregnancy, 6 months postpartum, and childhood)	Increased internalizing behaviors at 3 years of age and follow-up at 6 years of age
Brandlistuen *et al.* (11)	Matched siblings discordant for prenatal antidepressant exposure and concordant for no exposure assessed at 18 (discordant sibling n = 141, concordant sibling n = 20,039) and 36 (discordant sibling n = 112, concordant sibling n = 14,323) months	Yes (SCL-5 during pregnancy, 6 months postpartum, and lifetime history)	Increased anxiety symptoms at 36, but not 18, months after controlling for maternal depression
Hermansen *et al.* (37)	Prenatal SSRI–exposed (n = 28) and –unexposed (n = 42 born to mothers who had unmedicated depression during pregnancy, n = 33 born to healthy control mothers) 5- to 6-year-old children	Unclear (however, depression symptom measures during or after pregnancy did not differ between depressed mothers taking SSRIs and unmedicated depressed mothers)	Increased internalizing problems in SSRI-exposed, but not untreated depression, group, compared with healthy control subjects; however, the two exposure groups did not differ significantly on internalizing problems
Malm *et al.* (8)	Prenatal SSRI–exposed (n = 15,729) and –unexposed (n = 9651 born to mothers with unmedicated psychiatric disorders; n = 7980 whose mothers discontinued SSRI use prior to pregnancy; n = 31,394 born to mothers who never used SSRIs or had depression) children 0–14 years of age	No (attempted to approximate in-group comparisons and by excluding women using multiple psychotropic medications [which they argued is a proxy for severity])	Increased rates of depression from 12 years of age in SSRI-exposed group. No changes in rates of anxiety, ADHD, or autism.
Liu *et al.* (10)	Prenatal SSRI–exposed (n = 21,063) and –unexposed (n = 30,079 whose mothers discontinued SSRI use before pregnancy, n = 854,241 born to mothers who never used SSRIs) children 0 to 16.5 years of age	No (attempted to approximate in-group comparisons)	Increased risk of psychiatric disorders, including mood disorders, among children exposed prenatally to antidepressants compared with children whose mothers stopped taking them before pregnancy. However, the discontinuation group also had increased risk compared with the unexposed group.
Lupattelli *et al.* (12)	Prenatal SSRI–exposed (n = 290) and –unexposed (n = 3775 born to mothers with depression prior to or during pregnancy) children followed longitudinally from 1.5 to 5 years of age	Yes (SCL-5 or SCL-8 during pregnancy, childhood, and lifetime history)	Late-pregnancy SSRI exposure associated with increased anxious/depressed behaviors at 5 years of age
Rommel *et al.* (9)	Prenatal antidepressant–exposed (n = 15,892) and –unexposed (n = 27,096 whose mothers discontinued antidepressants before pregnancy) children 0–18 years of age	No (attempted to approximate in-group comparisons)	Increased risk for affective disorders for continuation group compared with discontinuation group (adjusted HR, 1.21). However, similar increased risk for paternal antidepressant use during pregnancy suggests that it may be due to parental psychopathology, rather than to antidepressant exposure.
Studies Reporting No Significant Association Between Prenatal SSRI Exposure and Internalizing Symptoms			
Nulman *et al.* (15)	Prenatal SSRI–exposed (n = 55) and –unexposed (n = 84) 1.3- to 2.5-year-old children	Unclear (did not report depression levels for control subjects)	No differences in temperament, mood, or behavior problems
Misri *et al.* (13)	Prenatal SSRI–exposed (n = 22) and –unexposed (n = 14) 4- to 5-year-old children	Yes (no unmedicated depression control group, but controlled for maternal mood [HDRS during pregnancy and childhood])	No significant differences in internalizing behaviors. Maternal depressive symptoms during childhood were significantly associated with parent-reported, but not clinician-reported, internalizing symptoms.
Oberlander *et al.* (17)	Prenatal SSRI–exposed (n = 33) and –unexposed (n = 42) 3-year-old children	Yes (HDRS during pregnancy and 3 months postpartum, BDI at 3 years postpartum)	No significant differences in internalizing behaviors when controlling for pre- and postnatal maternal depression. Maternal depression during childhood was significantly associated with increased internalizing symptoms.

Table 1. Continued

Study	Sample	Controlled for Maternal Depression?	Relevant Findings
Nulman *et al.* (14)	Prenatal SSRI–exposed (*n* = 62), prenatal venlafaxine–exposed (*n* = 62), and prenatal SSRI–unexposed (*n* = 54 born to mothers with untreated depression; *n* = 62 born to healthy control mothers) 3- to 7-year-old children	Yes (10-point visual analog scale during pregnancy and CES-D during childhood)	Antidepressant dose or duration did not predict internalizing symptoms. Maternal depression during pregnancy and follow-up was predictive.
Pedersen *et al.* (41)	Prenatal SSRI–exposed (*n* = 127) and –unexposed (*n* = 98 born to mothers with untreated prenatal depression; *n* = 723 born to mothers without prenatal depression or SSRI use) 4- to 5-year-old children	Yes (Mothers in untreated prenatal depression comparison group had more depressive symptoms during pregnancy and higher prevalence of depression at follow-up than the SSRI-exposed group. Secondary analyses also accounted for depression since childbirth.)	No significant differences in emotional symptoms (SDQ subscale). Children whose mothers had untreated prenatal depression had higher emotional symptom scores than the unexposed group, although this effect decreased when accounting for maternal psychiatric problems during childhood.
El Marroun *et al.* (42)	Prenatal SSRI–exposed (*n* = 69) and –unexposed (*n* = 376 born to mothers with untreated prenatal depression; *n* = 5531 born to healthy control mothers) children followed longitudinally from 1.5 to 6 years old	Yes (BSI depression scale during pregnancy and childhood)	No significant differences in affective problems. Children exposed to untreated prenatal depression had increased odds of affective problems.
Nulman *et al.* (39)	Siblings (*n* = 90), 3–7 years of age, discordant for prenatal SSRI exposure (*n* = 45 exposed, 45 unexposed)	Yes (10-point visual analog scale during pregnancy and postpartum and CES-D during childhood)	No significant differences in internalizing behaviors. Maternal depression during pregnancy and childhood was significantly associated with internalizing behaviors.
Grzeskowiak *et al.* (40)	Prenatal antidepressant–exposed (*n* = 210) and –unexposed (*n* = 231 born to mothers with unmedicated depression, *n* = 48,737 born to healthy control mothers) 7-year-old children	Yes (SCL-8d during pregnancy)	No significant differences in emotional symptoms after adjusting for maternal mood during pregnancy
van der Veere *et al.* (16)	Prenatal SSRI–exposed (*n* = 61) and –unexposed (*n* = 41) 2.5-year-old children	Yes (BDI during pregnancy and childhood)	No significant differences in internalizing symptoms. Maternal psychopathology during childhood was significantly associated with higher levels of internalizing problems.

SCL-5, SCL-8, and SCL-8d are short versions of the Hopkins Symptom Checklist reporting symptoms of anxiety and depression. Hanley *et al.* (38) used HDRS and BDI cutoff scores to create dichotomized variables for clinically significant depression.

ADHD, attention-deficit/hyperactivity disorder; BDI, Beck Depression Inventory; BSI, Brief Symptom Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; HDRS, Hamilton Depression Rating Scale; HR, hazard ratio; SCL, Hopkins Symptom Checklist; SDQ, Strengths and Difficulties Questionnaire; SRI, serotonin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

studies of brain volume in humans, which were conducted in neonates and produced conflicting findings (18,19).[1]

Evidence from nonhuman animal models suggests that prenatal SSRI exposure may induce depression by altering brain development [e.g., (20,21)]. As serotonin and other monoamines modulate key neurodevelopmental processes, manipulating serotonin during prenatal development may have widespread consequences. Nonhuman animal models have provided evidence that prenatal SSRI exposure may induce [e.g., increasing hippocampal neurogenesis (22)] and/or diminish [e.g., reducing S100B, which mediates neonatal neuronal outgrowth and survival (23)] neuronal growth; such variability could presumably influence child risk for depression and other mental health problems.

Given that SSRIs are one of the most commonly used forms of prescribed medication among pregnant women, and given a mixed literature suggesting that SSRI use during pregnancy may be associated with depression risk among offspring (Table 1), it is critical to further investigate this relationship as well as neural correlates. To this end, we used data from children (9–10 years of age) who completed the baseline session of the Adolescent Brain Cognitive

[1]One study (18) found no differences in global or regional brain volume between SSRI-exposed and unexposed (healthy control or untreated prenatal maternal depression) neonates (*N* = 204), while the other (19) found that SSRI-exposed neonates are characterized by larger gray matter volumes in the left occipital gyrus and right amygdala, insula, and superior frontal gyrus relative to healthy control subjects and infants exposed to untreated maternal depression (*N* = 98). Four additional diffusion tensor imaging studies have been conducted that yielded equivocal results. Two identified lower fractional anisotropy in several regions of prenatally exposed infants (18,57); one of these also found higher fractional anisotropy in other regions (57). A third also found both lower and higher fractional anisotropy in specific regions of exposed neonates' corpus callosa (47), while the fourth found increased white matter connectivity using a different approach (19) [for review, see (58)].

Development Study (ABCD Study) to test whether prenatal SSRI exposure is associated with depressive symptoms and brain structure metrics (i.e., gray matter volume, surface area, cortical thickness) during middle childhood. Given a prior mixed literature and considering that children were assessed during middle childhood, before heightened depression risk, we hypothesized that prenatal SSRI exposure may or may not be associated with increased depressive symptoms and variability in brain structure after considering important potential pregnancy (e.g., whether the pregnancy was planned), familial (e.g., socioeconomic status), and child (e.g., sex) factors. Given evidence that maternal depression during child development is associated with parenting practices linked to depression (24) as well as potential reporting biases (i.e., overreport of depression in others) (25), we examined whether any child outcomes associated with prenatal SSRI exposure were independent of maternal depression. Secondary analyses estimated associations between child depression and brain structure as well as associations between these variables and maternal depression, and child SSRI use.

METHODS AND MATERIALS

Participants

Data came from children (N = 11,875; mean age = 9.9 ± 0.6 years; 47.85% girls; 74.13% White) born between 2005 and 2009 to 9987 mothers through 10,801 pregnancies who completed the baseline session of the ongoing longitudinal ABCD Study (data release 2.0.1; https://abcdstudy.org/; http://doi.org/10.15154/1524692) (Supplement). All parents provided written informed consent after receiving a complete description of the study, and all children provided verbal assent to a research protocol approved by the institutional review board at each data collection site (n = 22) throughout the United States (https://abcdstudy.org/sites/abcd-sites.html).[2] Those with quality-controlled nonmissing structural MRI and prenatal SSRI exposure data were considered for analyses (n = 10,010) (Table 2). Analytic samples ranged from 5420 to 7528 after exclusions for missingness on covariates.

Measures

Data for all investigated variables are displayed in Table 2.

Prenatal Exposure to SSRIs and Other Medications

A parent or caregiver (89.1% biological mothers) retrospectively reported medications used by the mother during pregnancy, before and after maternal knowledge of pregnancy. A total of 280 (2.80%) children were reported to be prenatally exposed to SSRIs at some point during pregnancy, with 261 exposed prior to and 205 exposed following maternal knowledge of pregnancy. The majority of individuals were exposed both prior to and after maternal knowledge of pregnancy (n = 186); 75 were exposed only prior to maternal knowledge and 19 were exposed only after maternal knowledge of pregnancy. The average gestational age when mothers learned of their pregnancies was 6.91 ± 6.78 weeks.

Child Depressive Symptoms

The Depression DSM-5 Scale of the Child Behavior Checklist (26) was used to assess child depressive symptoms within the past 6 months according to parent/caregiver report.

Child Brain Structure

FreeSurfer v5.3 (http://surfer.nmr.mgh.harvard.edu/) was used to estimate global and regional structural MRI metrics. Global metrics included total brain volume, mean cortical thickness, and total cortical surface area. Regional metrics included cortical thickness and surface area for Desikan-Killiany cortical parcellation regions (n = 35/hemisphere, including hemisphere total) (27), as well as segmented subcortical volumes (n = 31, including left and right hemisphere cortical totals) (28). Acquisition and processing for the ABCD Study are described in the Supplement and (29,30), respectively. Briefly, 1-mm isotropic T1-weighted structural images were acquired from magnetization prepared rapid acquisition gradient-echo scans on 3T MRI scanners.

SSRI Exposure During Childhood

Caregivers reported whether the child took any prescribed medications within the past 2 weeks; 140 (1.4%) children were reported to have used SSRIs.

Maternal Depression

The parent/caregiver who completed the baseline questionnaires reported whether the child's biological mother had ever experienced depression. Caregivers also completed the Adult Self-Report questionnaire, which assesses their own past-6-month psychopathology, including depression; we used self-reported depression data (Adult Self-Report Depressive Problems DSM-5–Oriented Scale) from biological mothers only (n = 8842).

Covariates

The following variables were included as covariates in analyses: reported child sex; race (i.e., Asian, Black, mixed race, Native American or Alaskan, Native Hawaiian or Pacific Islander, Other, White); ethnicity (Hispanic/Latinx); age; birth weight; household income; maternal education; whether the pregnancy was planned; maternal age at birth; maternal lifetime history of depression; percentage of family members (biological parents, grandparents, siblings, aunts, and uncles) with a history of depression; prenatal exposure to prenatal vitamins, tobacco, marijuana, and alcohol; and whether the child had a reported twin or triplet in the study (Supplement). Additional analyses further included child polygenic risk for depression (in those of European ancestry only), child SSRI use, and recent maternal depressive symptoms (i.e., self-reported past-6-month depressive symptoms). For all imaging analyses, scanner ID was used instead of site ID as a grouping variable. Regional volume and surface area analyses also included intracranial volume to account for

[2]Cornell University was an original collection site that collected data from 34 participants, before being moved to Yale University. ABCD documentation reports 21 data collection sites and does not list Cornell; our analyses nested data based on 22 data collection sites, including the original Cornell site.

Table 2. ABCD Study Sample Characteristics

Variables	No Prenatal SSRI Exposure (*n* = 9730)	Prenatal SSRI Exposure			Total (*N* = 10,010)
		Before Maternal Knowledge of Pregnancy (*n* = 261)	After Maternal Knowledge of Pregnancy (*n* = 205)	Total (*n* = 280)	
Child Variables					
Age, years (*n* = 10,010)	9.92 ± 0.62	9.94 ± 0.64	9.93 ± 0.63	9.94 ± 0.64	9.92 ± 0.62
Sex, male (*n* = 10,007)	5071 (52.1%)	141 (54.0%)	120 (58.5%)	154 (55.0%)	5225 (52.2%)
Birth weight, ounces (*n* = 9735)	112.61 ± 23.24	106.49 ± 25.75	105.48 ± 25.70	106.99 ± 25.50	112.45 ± 23.32
Race/ethnicity (*n* = 10,010)					
Asian	574 (5.9%)	5 (1.9%)	5 (2.4%)	6 (2.1%)	580 (5.8%)
Black	2040 (21.0%)	17 (6.5%)	13 (6.3%)	18 (6.4%)	2058 (20.6%)
Hispanic	2071 (21.6%)	21 (8.1%)	14 (6.9%)	23 (8.3%)	2094 (21.2%)
Native American	303 (3.1%)	12 (4.6%)	8 (3.9%)	12 (4.3%)	315 (3.1%)
Pacific Islander	61 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	61 (0.6%)
Other	659 (6.8%)	10 (3.8%)	6 (2.9%)	11 (3.9%)	670 (6.7%)
White	7249 (74.5%)	252 (96.6%)	201 (98.0%)	269 (96.1%)	7518 (75.1%)
Intracranial volume, mm^3 (*n* = 10,005)	1,514,365 ± 148,156.5	1,545,173 ± 158,780.5	1,556,542 ± 158,297.4	1,547,026 ± 157,194.8	1,515,279 ± 148,506.5
Cortical thickness, mm (*n* = 10,005)	2.78 ± 0.10	2.80 ± 0.10	2.80 ± 0.096	2.80 ± 0.10	2.78 ± 0.10
Pregnancy and Family Variables					
Planned pregnancy (*n* = 9929)	5980 (62.0%)	171 (65.8%)	143 (70.1%)	184 (65.9%)	6164 (62.1%)
Maternal age at birth, years (*n* = 9887)	29.38 ± 6.20	31.27 ± 5.67	31.34 ± 5.33	31.27 ± 5.63	29.43 ± 6.19
Prenatal vitamin use (*n* = 9834)	9135 (95.6%)	248 (97.3%)	196 (98.0%)	267 (97.4%)	9402 (95.6%)
Household income (*n* = 9169)					
<$50,000	2661 (29.9%)	43 (17.4%)	30 (15.7%)	46 (17.4%)	2707 (29.5%)
$50,000–$74,999	1222 (13.7%)	40 (16.2%)	28 (14.7%)	42 (15.9%)	1264 (13.8%)
$75,000–$99,999	1288 (14.5%)	42 (17.0%)	30 (15.7%)	45 (17.0%)	1333 (14.5%)
$100,000–$199,999	2706 (30.4%)	93 (37.7%)	73 (38.2%)	97 (36.7%)	2803 (30.6%)
$200,000 or more	1028 (11.5%)	29 (11.7%)	30 (15.7%)	34 (12.9%)	1062 (11.6%)
Maternal education, years (*n* = 9656)	15.18 ± 2.61	16.04 ± 2.01	15.97 ± 2.00	16.04 ± 2.01	15.20 ± 2.60
Maternal dep history (*n* = 9651)	1983 (21.2%)	170 (65.6%)	124 (60.5%)	180 (64.7%)	2163 (22.4%)
Maternal recent dep symptoms (*n* = 8842)	53.74 ± 5.70	59.17 ± 7.67	58.87 ± 7.65	58.98 ± 7.63	53.89 ± 5.83
Family dep history, % (*n* = 9253)	11 ± 15	24 ± 20	23 ± 19	24 ± 20	11 ± 16
Twin/triplet in study (*n* = 10,010)	1789 (18.4%)	63 (24.1%)	51 (24.9%)	64 (22.9%)	1853 (18.5%)
Prenatal substance exposure before knowing of pregnancy					
Tobacco before (*n* = 9979)	1227 (12.6%)	34 (13.1%)	19 (9.3%)	36 (12.9%)	1263 (12.7%)
Alcohol before (*n* = 9690)	2281 (24.2%)	95 (37.0%)	69 (34.2%)	101 (36.7%)	2382 (24.6%)
Cannabis before (*n* = 9945)	492 (5.1%)	16 (6.2%)	8 (3.9%)	18 (6.5%)	510 (5.1%)
Prenatal substance exposure after knowing of pregnancy					
Tobacco after (*n* = 9997)	428 (4.4%)	11 (4.2%)	6 (2.9%)	11 (3.9%)	439 (4.4%)
Alcohol after (*n* = 9993)	216 (2.2%)	8 (3.1%)	8 (3.9%)	8 (2.9%)	224 (2.2%)
Cannabis after (*n* = 9995)	156 (1.6%)	5 (1.9%)	3 (1.5%)	6 (2.1%)	162 (1.6%)

Values are mean ± SD or *n* (%).
ABCD, Adolescent Brain Cognitive Development; dep, depression; SSRI, selective serotonin reuptake inhibitor.

total brain volume, while regional cortical thickness analyses included average whole-brain cortical thickness (Supplement).

Analyses

As the sample contained twin and nontwin siblings, as well as 22 research sites, linear mixed effect models were run using

the lme4 (version 1.1-21) package in R (version 3.6.0; R Foundation for Statistical Computing). Separate random-effects terms (random intercepts, fixed slope) were specified to group data by family ID and site/scanner. Prenatal SSRI exposure was represented as a fixed-effects grouping variable. All analyses accounted for the fixed-effect covariates described above. Estimates of ΔR^2 effect sizes were calculated using the MuMIn (version 1.43.17) R package (Supplement). Confidence intervals (CIs) (95%) were generated by computing likelihood profiles. The lmerTest package (version 3.1-1) was used to conduct 2-tailed tests of significance and obtain p values. Regression model diagnostics were evaluated, and models that violated assumptions (i.e., skewness, heteroscedasticity) of linear mixed-effect models were rerun using robust regression techniques (robustlmm R package, version 2.4-5) (31).

Primary Analyses: Prenatal SSRI Exposure. First, we estimated associations between prenatal SSRI exposure at any point during pregnancy and depressive symptoms in children. Second, we estimated whether prenatal SSRI exposure was associated with brain structure using a two-tiered analytic approach. Here, we first tested a priori regions of interest previously associated with adolescent and adult depression in the largest available meta analyses (n = 42) (32–34)[3,4]: hippocampus and amygdala volume; surface area in the lingual, superior frontal, postcentral, pericalcarine, lateral occipital, medial orbitofrontal, and precentral gyri and left and right hemispheres overall; cortical thickness in the medial orbitofrontal cortex, fusiform gyrus, insula, rostral anterior cingulate cortex, caudal anterior and posterior cingulate cortex, middle and inferior temporal gyrus, supramarginal gyrus, inferior frontal (pars opercularis) gyrus, and lingual gyrus. Multiple testing was corrected for using MatSpD (Matrix Spectral Decomposition), which accounts for the correlation between brain structure metrics to estimate the number of independent tests conducted (25 independent tests estimated; adjusted Bonferroni α level of 0.00205). Then, we conducted exploratory SSRI–brain structure analyses of all remaining 132 neural regional phenotypes available. MatSpD estimated 91.4 independent tests from 174 total tests (including a priori tests above) resulting in an adjusted Bonferroni α level of .000561 for exploratory analyses.

Significant associations were analyzed when excluding children who were currently taking SSRIs, who were exposed to illicit substances prenatally, who were born at extreme levels of prematurity, or whose biological mothers were not the parent/caregiver respondent (Supplement). Any significant associations were also subsequently examined when stratified according to the timing of prenatal SSRI exposure (before/after maternal knowledge of pregnancy) and commonly used specific SSRIs (i.e., sertraline n = 118, fluoxetine n = 68, escitalopram n = 54) as well as when controlling for recent maternal depressive symptoms and child SSRI use. Finally, to account for potential confounding effects of genomic liability not accounted for by familial density of depression and maternal lifetime depression, we examined significant associations when accounting for child polygenic risk scores for depression in the European ancestry subsample (Supplement). To evaluate the specificity of any significant findings, we tested whether prenatal exposure to the antidepressant bupropion (n = 63), antihistamines (n = 78), or prescription opioid pain medications (n = 100) were associated with variability in phenotypes linked to prenatal SSRI exposure in post hoc analyses (Supplement).

Secondary Analyses. As variability in neural phenotypes are hypothesized to indirectly link depression risk factors to depression (even in the absence of main effects), we explored whether child brain structure is associated with child depression (Supplement). Finally, we evaluated whether maternal depression or child SSRI use were associated with child depression and brain structure (Supplement).

RESULTS

Prenatal SSRI Exposure and Child Depression Outcomes

Prenatal SSRI exposure (n = 235)[5] was associated with a small increase in depressive symptoms among children, after accounting for covariates previously described (b = 1.18 [95% CI, 0.44 to 1.93], t = 3.11, ΔR^2 = 0.0013, p = .0019) (Figure S1, Table S1). Although model diagnostics identified violations of model assumptions (i.e., residual normality and homoscedasticity), a robust regression model that does not require such assumptions produced similar results (b = 0.78, t = 3.16).

Post hoc regressions revealed that this association (see Supplement) 1) was primarily driven by prenatal SSRI exposure before (n = 219; b = 1.16, ΔR^2 = 0.0012, p = .0032) but not after (n = 172; b = 0.84, ΔR^2 = 0.00054, p = .056) maternal knowledge of pregnancy; 2) was present for sertraline (n = 118; b = 2.39, ΔR^2 = 0.0013, p = .000050), trending for fluoxetine (n = 68, b = 1.32, ΔR^2 = −0.0014, p = .11), and absent for escitalopram (n = 54; b = 0.49, ΔR^2 = −0.0024, p = .57); 3) remained when controlling for child SSRI use and when excluding children who were currently taking SSRIs, who were exposed prenatally to illicit substances, who were born very prematurely, or whose biological mother was not the caregiver respondent; 4) was largely unaltered in effect size when accounting for child polygenic

[3]The adolescent/adult depression literature was relied on owing to the limited available literature on SSRI exposure and brain structure as well as on childhood depression.

[4]Regions were explored bilaterally in our analyses, regardless of whether the original finding was lateralized. Owing to the important role of the amygdala in processing emotionally salient stimuli as well as associations with SSRI exposure, we included this as an a priori region of interest despite its trending association in a meta-analysis of depression (p = .09).

[5]While the overall sample with nonmissing prenatal medication and MRI data (n = 10,010) contained 280 children with prenatal SSRI exposure before or after maternal knowledge of pregnancy, the analytic sample used in this regression after listwise deletion of subjects with missing data contained 235 children with prenatal SSRI exposure before or after maternal knowledge of pregnancy.

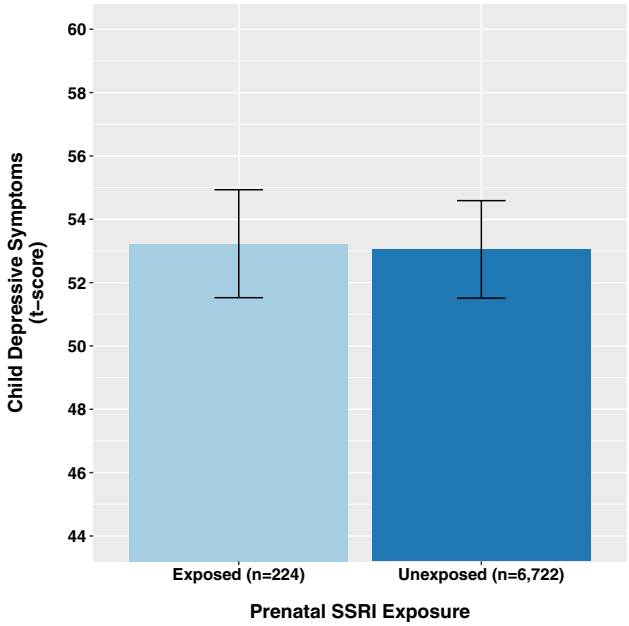

Figure 1. Children prenatally exposed to selective serotonin reuptake inhibitors (SSRIs) do not have elevated depressive symptoms when accounting for recent maternal depressive symptoms. Depression symptom measure: Child Behavior Checklist. Error bars represent 95% confidence intervals. The *n*s represent the analytic sample included in the regression analysis after listwise deletion for missing covariate data. Estimated marginal means were extracted from mixed-effects models that controlled for all covariates, including lifetime history and recent maternal depression, and the dependency in the data.

risk for depression, though no longer significant owing to sample size reductions; and 5) was no longer significant when including recent maternal depressive symptoms in the model (b = 0.179, p = .63) (Figure 1).[6]

Prenatal SSRI Exposure and Child Brain Outcomes

Nominally significant findings are reported in the Supplement.

Analyses of A Priori Depression Regions of Interest. Prenatal SSRI exposure was not significantly associated with any a priori brain structure phenotypes after correction for multiple testing (all ps > .002) (Table S2).

[6]Our consideration of recent maternal depressive symptoms was limited to children whose biological mother brought them in for the study visit (n = 8842 out of 10,010; analytic n following listwise deletion = 6946); nonetheless, this reduction in sample size alone was not responsible for attenuating the association between child depression and prenatal SSRI exposure, as restricting our analyses to this subset but not including recent maternal depression symptoms resulted in significant associations between prenatal SSRI exposure and child depression (b = 1.16, p = .0035). Further, the percentage of the analytic sample exposed prenatally to SSRIs was nearly identical in the original and post hoc analyses (3.1% and 3.2%, respectively).

Exploratory Analyses in All Brain Regions of Interest. Prenatal SSRI exposure was associated with a thicker left lateral occipital cortex (b = 0.0272 [95% CI, 0.0153 to 0.0392] mm, t = 4.47, ΔR^2 = 0.0011, p = .0000079) (Figure 2A; Figure S1, Tables S1 and S2) and larger left superior parietal surface area (b = 145.3 [95% CI, 65.4 to 225.2] mm^2, t = 3.55, ΔR^2 = 0.00095, p = .00038) (Figure 2B; Figure S1, Tables S1 and S2) after correction for multiple testing. These findings remained significant both before and after maternal knowledge of pregnancy and when accounting for recent maternal depressive symptoms and child depression polygenic risk scores, as well as when excluding children who were currently taking SSRIs, who were exposed prenatally to illicit substances, who were born very prematurely, or whose biological mother was not the caregiver respondent (Supplement). When considering SSRI type (Table S3), nominally significant associations were present for all but fluoxetine and the left superior parietal surface area; only the association between escitalopram exposure (n = 54) and a thicker left lateral occipital cortex survived multiple testing correction (b = 0.069 [95% CI, 0.042 to 0.097] mm, t = 4.99, ΔR^2 = 0.00075, p = .00000063).

Prenatal Exposure to Other Medications and Child Depression and Brain Outcomes

Prenatal exposure to bupropion (n = 63), antihistamines (n = 78), and prescription pain medication (n = 100) was not significantly associated with child depressive symptoms or brain structure (Supplement).

Secondary Analyses

Child Brain Structure and Depressive Symptoms. Neither the left lateral occipital cortex thickness nor the left superior parietal surface area, which were associated with prenatal SSRI exposure (see above), was associated with child depression symptoms (b = −0.47 mm, p = .50; and b = −0.00 mm^2, p = .25; respectively). A smaller total bilateral surface area was associated with more child depressive symptoms (total: b = −0.0000168, ΔR^2 = 0.0017, p = .000115; left: b = −0.0000320, ΔR^2 = 0.0015, p = .000236; right: b = −0.0000345, ΔR^2 = 0.0018, p = .0000612) (Figure S2). Exploratory analyses revealed that child depressive symptoms were also significantly associated with total brain volume (b = −0.00000270, ΔR^2 = 0.0023, p = .000115) as well as with left and right hemisphere cortical volume (left: b = −0.0000109, ΔR^2 = 0.0018, p = .0000622; right: b = −0.0000112, ΔR^2 = 0.0019, p = .0000409) (Figure S2, Table S4).

Maternal Depression and Child SSRI Use. Maternal depression and child SSRI use were significantly associated with greater child depressive symptoms. Results, including associations with child brain structure, are reported in the Supplement.

DISCUSSION

Two primary findings emerged from our investigation of retrospectively reported prenatal SSRI exposure, depression, and brain structure during middle childhood. First, we found that prenatal SSRI exposure was associated with a small increase in depressive symptoms during middle childhood but

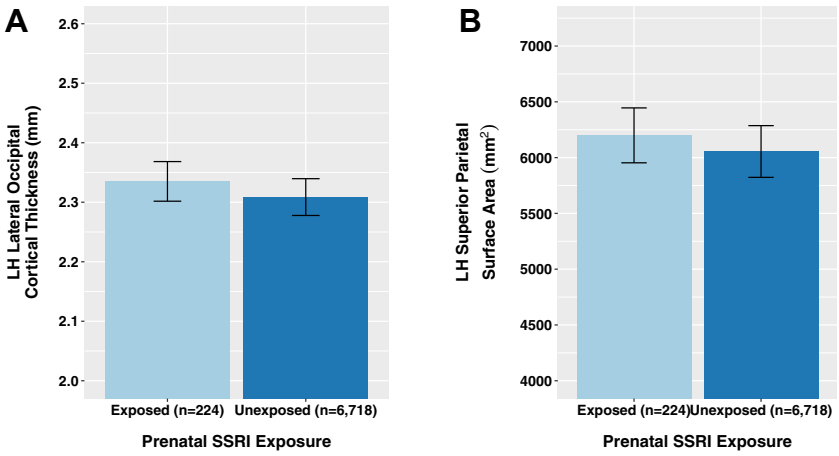

Figure 2. Children prenatally exposed to selective serotonin reuptake inhibitors (SSRIs) have a thicker left lateral occipital cortex and larger left superior parietal surface area. Error bars represent 95% confidence intervals. The *n*s represent the analytic samples included in the regression analyses after listwise deletion for missing covariate data. Estimated marginal means were extracted from mixed-effects models that controlled for all covariates, including lifetime history and recent maternal depression, and the dependency in the data. LH, left hemisphere.

that this association was not independent of recent maternal depressive symptoms. Second, prenatal SSRI exposure was associated with larger surface area in the left superior parietal region and thicker left lateral occipital cortex. However, this variability in brain structure was not associated with child depressive symptoms, and effect sizes were small. Given risks associated with prenatal exposure to maternal depression (35) and the effectiveness of treating depression during pregnancy with SSRIs (36), our data suggest that concern for depression during middle childhood following SSRI exposure should not discourage SSRI use during pregnancy. Nonetheless, this sample did not extend into peak periods of depression onset, and we did not study other adverse effects that have been associated with SSRI exposure, which are important avenues for future research.

Prenatal SSRI Exposure and Depressive Symptoms During Middle Childhood

The initial link we observed between prenatal SSRI exposure and a small elevation in depressive symptoms in children was robust to the inclusion of lifetime history of maternal depression and depression density among first-degree relatives but not to recent (i.e., past 6 months) maternal depressive symptoms. Associations were most prominent for sertraline, which was the most commonly used SSRI in this sample. Notably, this association was not robust to the inclusion of current maternal depressive symptoms after multiple testing correction and did not differ from fluoxetine (*b* estimates residing within 95% CIs) (see Supplement). Even before considering current maternal depression in our models, bupropion exposure was not significantly associated with child depression; whether this is suggestive of potential SSRI-related effects or attributable to the limited power of our bupropion (n = 63 exposed) analyses remains unclear.

Our observations contrast with large studies showing that prenatal SSRI exposure is associated with elevated risk for depression or internalizing symptoms (Table 1) (8–12). Notably, over half of these studies did not explicitly model any form of maternal depression in analyses (8–10,37), and only a few (12,38) evaluated recent maternal depressive symptoms. Along these lines, our observations mirror prior null associations observed for child internalizing symptoms at younger ages in studies that accounted for maternal depression during pregnancy and childhood (13–17,39–42). However, the vast majority of these studies would be underpowered to detect the effect size we observed here, prior to the inclusion of recent maternal depressive symptoms. That recent maternal depressive symptoms, but not lifetime history of maternal depression and familial density of depression, accounted for the significant association between prenatal SSRI exposure and child depressive symptoms highlights potential depressogenic effects of postnatal rearing environments associated with maternal depression, which has been well documented in the literature (24). Indeed, recent maternal depressive symptoms explained 11% of the variance in child depressive symptoms, while prenatal SSRI exposure explained only 0.13%. However, it is also possible that the association between recent maternal depression symptoms and maternal-rated child depression is inflated due to potential reporting biases [i.e., overreport of depression in others (25)]. These findings highlight the importance of considering maternal depression at the time of report and during childhood in the context of prenatal SSRI exposure.

Experimental nonhuman animal studies have found evidence that prenatal SSRI exposure is depressogenic (43). However, our associations, before controlling for recent maternal depression, are discrepant with regard to timing of exposure and offspring assessment in these models. For example, one study of mice found that exposure during the equivalent period of the third trimester in humans was associated with depressive-like behaviors during late adolescence/young adulthood (43). Our observed association was restricted to exposure prior to maternal knowledge of pregnancy, which occurred on average well before the third trimester (6.8 weeks). The lack of association between SSRI exposure following maternal knowledge of pregnancy and child depression further reduces the potential clinical utility of discontinuing treatment upon pregnancy awareness, at least with regard to depression. As nonhuman animal models and some human studies [e.g., (8)] suggest that the depressogenic effects of prenatal SSRI exposure do not emerge until later adolescence, it remains plausible that effects will be larger and observed for

different timings of exposure at later developmental stages (e.g., late adolescence, young adulthood), when depression risk rises.

Given that prenatal SSRI exposure was not independently associated with child depressive symptoms, when considering recent maternal depression, our findings suggest that effectively treating maternal depression is crucial to minimize adverse effects on children. In addition to antidepressants, empirically supported psychotherapies represent another first-line treatment option for pregnant women and mothers (44). Digital administration of psychotherapy, which was recently shown to reduce depression, anxiety, and stress during pregnancy and the postpartum period in a meta-analysis of randomized controlled trials, may increase accessibility and reduce barriers (45).

Prenatal SSRI Exposure and Brain Structure During Middle Childhood

If prenatal SSRI exposure influences child behavior, it would presumably do so by influencing the brain. For instance, prenatal SSRIs lead to decreases in S100B, a protein that mediates neonatal neuronal outgrowth and survival (23). However, we found limited evidence that prenatal SSRI exposure is associated with gray matter–related brain structure (i.e., volume, cortical thickness, and surface area) during middle childhood. Indeed, only left superior parietal surface area and left lateral occipital cortical thickness were significantly associated with prenatal SSRI exposure after accounting for multiple testing; these effects were small (both ~0.1%) and in the direction of increased size, which would not align with the S100B hypothesis. Additionally, these regional metrics have not been significantly associated with major depressive disorder among adolescents or adults in recent large meta-analyses (32,34). Of note, however, infant studies have also found increased brain structure (i.e., volume) (19) and functional connectivity (46) in the left occipital cortex, as well as left-lateralized microstructural alterations (47), of infants prenatally exposed to SSRIs. Post hoc analyses stratified by the type of SSRI exposure yielded limited evidence for specificity (Supplement). In the present study, prenatal SSRI exposure was not associated with child depressive symptoms, independent of recent maternal depressive symptoms, precluding an interpretation of any mediating or moderating effects of brain structure. Still, it remains possible that the small brain structure differences we observed may be associated with subsequent depression, or that SSRI exposure and its correlates are associated with regional brain structure during earlier and/or later development.

Secondary Analyses: Brain Structure, Depressive Symptoms, and SSRI Use Among Children

Depressive symptoms during middle childhood were associated with smaller global brain structure (i.e., total surface area and brain volume). Much like the other associations we observed, these effects were small, accounting for <0.25% of variance in depressive symptoms. Inconsistent with prior studies (32–34), we found no evidence of regional associations; this divergence may be attributable to the relatively younger age of our sample [but see also, e.g., (48)]. Although maternal depression and child SSRI use were unsurprisingly associated with greater child depressive symptoms, only child SSRI use was associated with brain structure. Children taking SSRIs had increased right isthmus cingulate surface area. Interestingly, maternal depression (lifetime or recent) was not significantly associated with child SSRI use.

Limitations

Some study limitations are noteworthy. First, we relied on ~10-year retrospective report of SSRI use during pregnancy, which may result in misclassification (49). Data suggest that retrospective assessment of psychotropic medication use during pregnancy does not differ from prospective assessment during pregnancy (50), and reported SSRI use shows strong concordance with pharmacy and medical records (51,52). In the ABCD Study, 2.8% of children had mothers who were reported to have used SSRIs during pregnancy, which is on the lower end of prevalence estimates in the United States during their time of birth, which range from 2.6% to 15% (3,4), suggesting the potential for recall or ascertainment biases that may have influenced our observations. Large longitudinal studies, such as the upcoming HEALthy Brain and Child Development Study (53), which plans to recruit over 7000 pregnant women and follow their children with extensive phenotyping, will be critical to further understand associations with prenatal SSRI exposure.

Second, our study is cross-sectional and does not follow children into peak depression risk (i.e., later adolescence–young adulthood) (54). As such, it remains possible that child depression and brain structure or longitudinal trajectories of these variables are associated with prenatal SSRI exposure. As the ABCD Study will follow recruited children through adolescence and into young adulthood, future studies will have the opportunity to conduct longitudinal analyses as children enter the period of developmental risk for depression. Third, although this represents the largest study of prenatal SSRI exposure, brain structure, and depression during middle childhood to our knowledge, our power was limited by a proportionally small number of participants exposed to SSRIs prenatally, especially for analyses of exposure timing (i.e., before or after maternal knowledge of pregnancy); this is likely compounded by unmeasured heterogeneity (e.g., duration) in exposure.

Fourth, despite modeling many familial, pregnancy, and child-related variables that may potentially confound associations, the potential role of unmeasured confounds or alternative derivations cannot be discounted. For example, only 180 of the 280 mothers who took SSRIs during their pregnancy had a reported lifetime history of depression, so it is possible that other medical conditions not accounted for in our models may impact results. Further, while we included lifetime maternal depression, first-degree relative lifetime depression density, child polygenic risk for depression, and recent maternal depressive symptoms in our analyses, we were unable to estimate potential associations between maternal depression during pregnancy and child outcomes in our models, as these data were not collected. Some prior studies have found that perinatal depression, but not prenatal SSRI exposure, is associated with childhood internalizing

symptoms (13,14,16,39–42). Fifth, as is standard practice for this age of children, we relied on caregiver report of child depression, and there is some evidence that unlike externalizing symptoms, internalizing symptoms may not be well captured by observer report (55). Sixth, the analyzed dataset contained limited data on the timing of antidepressant exposure (i.e., pre- and postmaternal knowledge of pregnancy), which limits our ability to examine time-dependent associations (12).

Conclusions and Clinical Implications

These data suggest that potential risk for depression during middle childhood should not dissuade the use of SSRIs during pregnancy. Specifically, our observed associations were small in magnitude, and the link between prenatal SSRI exposure and child depressive symptoms was not independent of recent maternal depressive symptoms. Considering adverse offspring outcomes associated with maternal depression during pregnancy (56) and increased risk of relapse following SSRI discontinuation during pregnancy (36), these findings assuage concerns regarding depression risk in middle childhood among offspring prenatally exposed to SSRIs. Nonetheless, this sample did not extend into peak periods of depression onset, and we did not study other adverse effects that have been associated with SSRI exposure. It will be important for future work to follow children into peak periods of risk to further evaluate potential associations between prenatal SSRI exposure, brain structure, and depression.

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