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WASHINGTON UNIVERSITY IN ST. LOUIS

Department of Psychological and Brain Sciences

Associations Between Prenatal Selective Serotonin Reuptake Inhibitor Exposure, Depression and Brain Morphology in Middle Childhood

by

Allison Moreau

A thesis presented to
The Graduate School
of Washington University in
partial fulfillment of the
requirements for the degree
of Master of Arts

December 2019
St. Louis, Missouri

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Allison Moreau

Washington University in St. Louis

December 2019

Dedicated to my parents, Marc and Kathy, and my sisters, Andrea and Ashley.

ABSTRACT OF THE THESIS

Associations Between Prenatal Selective Serotonin Reuptake Inhibitor Exposure, Depression and Brain Morphology in Middle Childhood

by

Allison Moreau

Master of Arts in Psychological and Brain Sciences

Washington University in St. Louis, 2019

Objective: Selective Serotonin Reuptake Inhibitors (SSRIs) are one of the most widely used prescribed medicine by pregnant women. A mixed literature suggests that prenatal SSRI exposure may increase depression risk among offspring.

Method: Using data from children (n=11,076) who completed the baseline session of the Adolescent Brain and Cognitive Development (ABCD) study, we examined whether prenatal exposure to SSRIs is associated with child depression and variability in depression-related brain structures (i.e., hippocampus, amygdala, nucleus accumbens, caudate, putamen; rostral anterior cingulate; rostral and caudal middle frontal, superior frontal, and lateral and medical orbitofrontal cortices). Analyses were cross-sectional and included the following covariates: sex, race, ethnicity, age, birthweight, household income, maternal education, whether pregnancy was planned, gestational age when mother aware of pregnancy, prenatal exposure to prenatal vitamins, tobacco, marijuana, and alcohol. Lifetime maternal depression was included when not the independent variable of interest, and intracranial volume was included for brain structure analyses.

Results: Prenatal SSRI exposure and maternal depression were each independently associated with depressive symptoms among children. No gray matter-based imaging metrics were associated with SSRI exposure following correction for multiple testing. SSRI exposure was nominally associated with reduced caudate, amygdala, and hippocampal volumes (all ps <0.045). Conclusion: We find evidence that prenatal SSRI exposure is associated with elevated depressive symptoms among children, even after accounting for lifetime maternal depression. Imaging derived metrics of gray matter (i.e., subcortical volume, cortical thickness of brain regions associated with depression) may not play a mechanistic role in prenatal SSRI exposure-related offspring depression risk.

Chapter 1: Introduction

Over the past 2 decades, national survey data indicate that the use of antidepressant medication increased by 594% in the United States. Between 2011-2014, 10.7% of the United States population reported using an antidepressant medication in the past 30 days, compared to 1.8% of the population between 1988-1994 (Center for Health Statistics, 2017). As women are at greater risk than men for depression, and the time period corresponding to reproductive years is associated with the greatest risk, it is perhaps unsurprising that among the 50% of pregnant women taking prescribed medication Selective Serotonin Reuptake Inhibitors (SSRIs) are among the most commonly used classes of medication. In 2008, over 7% of pregnant women in the US took them at some point during pregnancy (Mitchell et al., 2011). However, the impact of prenatal SSRI exposure on children is poorly understood. Prenatal SSRI exposure has been associated with a host of adverse physical outcomes (e.g., diminished fetal growth, hypertension) (Yonkers, Blackwell, Glover, & Forray, 2014), with mixed evidence that it may (e.g., Brandlistuen et al., 2015; Hanley, Brain, & Oberlander, 2015; Hermansen, Røysamb, Augusti, & Melinder, 2016; Liu et al., 2017; Lupattelli et al., 2018; Malm et al., 2016) or may not (e.g., Grzeskowiak et al., 2016; Misri et al., 2006; Nulman et al., 2012, 2015, 1997) predispose offspring to depression, even when considering maternal depression. Given that SSRIs represent one of the most commonly used forms of prescribed medication among pregnant women, and a mixed literature suggesting that prenatal SSRI exposure may be associated with depression risk among offspring, it is critical to further investigate this relationship as well as the neural mechanisms that may underlie it.

Initial studies (n=2) comparing offspring (ages 1.3-5) born to depressed mothers who used SSRIs during pregnancy (Ns=22, 55) to nondepressed mothers who did not (Ns=14, 84) found no difference in depression and related behavior among offspring (Misri et al., 2006; Nulman et al., 1997); (reviewed in Gentile & Galbally, 2011). These initial null findings have been followed by mixed data from humans and non-human animal models that SSRI exposure may or may not increase risk for depression and related behavior among offspring. In rodents, perinatal SSRI exposure (equivalent to the third trimester in humans) is associated with elevated depressive-like behavior in later adulthood (Ansorge et al., 2004). Suggestive of potential conservation across species, some recent human studies (Ns ranging from 28-44 exposed children; child ages ranging from 3-15) have reported that children exposed to SSRIs prenatally are at increased risk for depression and internalizing psychopathology (Hanley et al., 2015; Hermansen et al., 2016; Liu et al., 2017; Lupattelli et al., 2018; Malm et al., 2016). Notably, some of these studies controlled for maternal mood during pregnancy and childhood (Hanley et al., 2015) or included an unexposed depressed control group (Hermansen et al., 2016) suggesting that the association between SSRI exposure and offspring depression may be independent of depression exposure during pregnancy. Such speculation is further supported by a sibling-matched control study that found that offspring who were exposed to SSRIs displayed greater anxiety symptoms at 3 years, but not 18 months, than their unexposed siblings (Brandlistuen et al., 2015). As this study matched mothers, it provides the most compelling evidence of a potential impact of prenatal SSRI exposure on internalizing symptoms in humans. At the same time, another sibling-matched control study found no differences in internalizing behavior between exposed and unexposed siblings that ranged in age from 3-7 years old (Nulman et al., 2015). Further, other recent studies that have included unexposed depression control groups have

found no evidence that prenatal SSRI exposure (Ns: 62-210) is associated with depression by ages 3-7 (Grzeskowiak et al., 2016; Nulman et al., 2012). Collectively, there is mixed evidence suggesting that SSRI exposure may or may not be independently associated with depression risk among offspring.

In contrast to this sizable body of literature looking at prenatal SSRI exposure and offspring depression, there is a limited literature examining associations between prenatal SSRI exposure and offspring brain structure. This is unfortunate because non-human animal models suggest that SSRIs may contribute to risk for depression in offspring by altering brain development (e.g., Gingrich et al., 2017). Indeed, we are only aware of two such human studies, which were conducted in neonates and produced conflicting findings (Jha et al., 2016; Lugo-Candelas et al., 2018). Jha and colleagues (2016) found no differences in global or regional brain volume between SSRI-exposed and unexposed (healthy control or untreated prenatal maternal depression) neonates (total N=204), while Lugo-Candelas and colleagues (2018) found increased gray matter volume in the right amygdala and insula and left superior frontal and occipital gyri for SSRI-exposed infants compared to healthy controls and infants exposed to untreated maternal depression (total N=98).

In the present study, we examined whether self-reported maternal use of SSRIs is associated with brain structure (volume and cortical thickness) and depressive symptoms among the 11,875 children (average age 10) who participated in the baseline Adolescent Brain Cognitive Development (ABCD) study. Regions of interest that have been previously associated with depression were selected for a priori analyses: cortical regions of rostral anterior cingulate, caudal and rostral middle frontal gyri, superior frontal gyrus, and medial and lateral orbitofrontal

cortex and the subcortical regions hippocampus, amygdala, nucleus accumbens, caudate and putamen (Schmaal et al., 2017, 2016; Wise, Cleare, Herane, Young, & Arnone, 2014).

We hypothesize that SSRI exposure will be associated with reduced volume and cortical thickness across ROIs. Given that participants have yet to enter peak periods of risk for Major Depressive Disorder, adolescence, (Kessler, Avenevoli, & Ries Merikangas, 2001), we hypothesize that exposure may or may not be associated with increased psychopathology symptomatology.

Chapter 2: Methods

2.1 Participants

Data came from children (n=11,875; M_{age} = 9.9±0.6 years; 47.85% girls; 74.13% White) born between 2005 and 2009 to 9,987 mothers through 10,801 pregnancies who completed the baseline session of the ongoing longitudinal Adolescent Brain Cognitive Development (ABCD) study (data release 2.0.1; https://abcdstudy.org/). The study includes a family-based design in which twin (n=2,108), triplet (n=30), non-twin siblings (n=1,589), and singletons (n=8,148) were recruited. All parents provided written informed consent, and all children provided verbal assent to a research protocol approved by the institutional review board at each data collection site (n=22)[1] throughout the United States (https://abcdstudy.org/sites/abcd-sites.html). For our analyses, participants who had quality-controlled non-missing structural MRI data were included (N=11,076; aged 9-10 years old; 48% female; 74.8% of European ancestry; 20.8% of African ancestry; 6.1% of Asian ancestry; 10.5% other ancestry; **Table 1**). A total of 299 children (2.70%) were exposed to SSRIs prenatally.

2.2 Measures

2.2.1 Prenatal Medication Exposure

A parent or caregiver (91.5% mothers) retrospectively reported medications used by the mother during pregnancy, before and after maternal knowledge of pregnancy. We coded medication use according to categories (**Table 2**), including selective serotonin reuptake inhibitors (SSRIs).

[1] 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.

2.2.2 Child Structural MRI

ABCD study imaging acquisition protocol and parameters as well as image processing and analysis methods are described in detail in Casey et al. (2018) and Hagler et al. (2019), respectively. Briefly, 1 mm isotropic T1-weighted structural images were acquired from magnetization-prepared rapid acquisition gradient echo scans on 3 T (Siemens, Phillips and GE) MRI scanners using either a 32-channel head or 64-channel head-and-neck coil. Scan protocols were carefully harmonized across the three MRI vendor platforms to reduce scanner-related variability. Head motion is a significant concern for pediatric imaging, so real-time motion detection and correction was implemented (prospective motion correction (PROMO; (White et al., 2010)) on the GE and Volumetric Navigators (vNav; (Tisdall et al., 2016)) on the Siemens platforms). MRI data was processed with the Multi-Modal Processing Stream software package that includes FreeSurfer 5.3 (Dale, Fischl, & Sereno, 1999; Fischl et al., 2002; Fischl, Sereno, & Dale, 1999). Besides a modified intensity normalization process used by the ABCD processing pipeline, the standard FreeSurfer cortical and subcortical reconstruction pipeline was run to generate structural measures including volume and cortical thickness. Only participants whose structural MRI reconstructions passed QC tests (n=11,076) were included in the current analysis (see Hagler et al., 2019).

Subcortical volume was investigated using the automatic subcortical segmentation in FreeSurfer 5.3 for the left and right hippocampi, amygdalae, nucleus accumbens, caudate and putamen (total n=10; **Table 1**). Cortical thickness was investigated using the Desikan-Killiany cortical parcellation map in FreeSurfer 5.3 (Desikan et al., 2006) for the average whole brain, as well as the following ROIs previously associated in the literature with depression: rostral anterior

cingulate, rostral and caudal middle frontal cortex, superior frontal cortex, and lateral and medial orbitofrontal cortex (total regional cortical thickness n=12; **Table 1**).

2.2.3 Child Depressive Symptoms

The Child Behavior Checklist (CBCL) was completed by parents/guardians, which provides dimensional measures of the child depressive symptoms (Depression DSM-5 Scale; **Table 1**). The Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-5) was administered to the children to determine psychiatric diagnoses, including Major Depressive Disorder, Persistent Depressive Disorder, and Unspecified Depressive Disorder (**Table 1**).

2.2.4 Psychopathology in Mothers

Two potential sources of information regarding maternal psychopathology were obtained in the ABCD Study. First, the parent, guardian or other caretaker who completed the baseline questionnaires was asked whether the child's biological mother, as well as other family members, ever experienced a host of psychiatric disorders. Second, the caregiver also completed the Adult Self-Report (ASR) questionnaire, which includes scales for various psychiatric syndromes and disorders occurring in the past six months. For 10,131 children, the person filling out the questionnaires was the biological mother; thus, 10,131 children also had maternal ASR data. Given the topic and objective of this report, maternal depression was the only psychopathology investigated in both of these data sources (**Table 1**).

2.2.5 Covariates

The following variables were considered as covariates in analyses: reported child sex, race, ethnicity, age, birthweight, as well as household income, maternal education, lifetime maternal depression (when this was not the independent variable of interest), whether the pregnancy was planned, at what gestational age the mother became aware of the pregnancy, and prenatal

exposure to prenatal vitamins, tobacco, marijuana, and alcohol (**Table 1**). For all imaging analyses, intracranial volume (ICV) was included to account for total brain volume (**Table 1**).

2.3 Analyses

As the sample contains twin and non-twin siblings, as well as 22 research sites,[2] linear mixed effect models were used to nest data on these parameters using the lme4 (version 1.1-21) package in R (version 3.6.0). Our primary analyses examined whether prenatal SSRI exposure (i.e., before or after maternal knowledge of pregnancy, n=299) was associated with child brain structure (i.e., regional subcortical volumes, n=10; regional cortical thickness, n=12 + whole brain cortical thickness) and depressive symptoms (i.e., CBCL DSM-5 Depression Scale). Covariates included in these analyses included: child variables (i.e., child gender, race [i.e., White/not White, Black/not Black, Asian/not Asian, Native Hawaiian or Pacific Islander/not Native Hawaiian or Pacific Islander, Native American or Alaskan/not Native American or Alaskan, Other/not Other] and ethnicity (Hispanic/not Hispanic), age, birthweight), maternal/familial variables (i.e., household income, maternal education, lifetime maternal depression), and pregnancy/maternal-related variables (i.e., whether the pregnancy was planned, at what gestational age the mother learned of the pregnancy, and maternal use of alcohol, tobacco, and marijuana before and after knowledge of pregnancy as well as prenatal vitamin use). Analyses of brain structure also included intracranial volume (ICV) as a covariate. Multiple testing was adjusted for using Benjamini Hochberg False Discovery Rate (FDR_{BH}) correction within each brain structure phenotype (i.e., subcortical volumes, n=10; cortical thickness, n=13).

[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.

Following null associations between prenatal SSRI exposure and brain structure (see **Results**), we subsequently explored whether the timing of SSRI exposure contributed to differences and tested whether SSRI use during pregnancy before or after knowledge was associated with brain structure in a series of independent regressions; FDR_{BH} was used to adjust for multiple testing here (subcortical brain structure: 20 tests; cortical thickness: 26 tests).

Secondary analyses examined whether lifetime maternal depression or current maternal depressive symptoms are correlated with brain structure or depressive symptoms in children and further whether child depressive symptoms were correlated with brain structure. For each of these outcomes, the same covariates were used with the exception that any antidepressant exposure (before or after maternal knowledge of pregnancy) was added as a covariate to the maternal depression analyses. Multiple testing was adjusted for using FDR_{BH} (maternal depression and child brain structure each had the following number of tests: maternal depression: n=2, subcortical volumes: n=10, cortical thickness: n=13).

Chapter 3: Results

3.1 Prenatal SSRI exposure and child depression outcomes

Prenatal SSRI exposure was associated with increased depressive symptoms among children (b=0.95, p = 0.01; **Figure 1**; **Table 2**). *Post hoc* analyses revealed that prenatal SSRI exposure before, but not after, maternal knowledge of pregnancy was associated with increased depressive symptoms among children (before: b=1.101, p=0.0093, p_{FDR} = 0.0186; after: b=0.35, p = 0.42, p_{FDR} = 0.42).

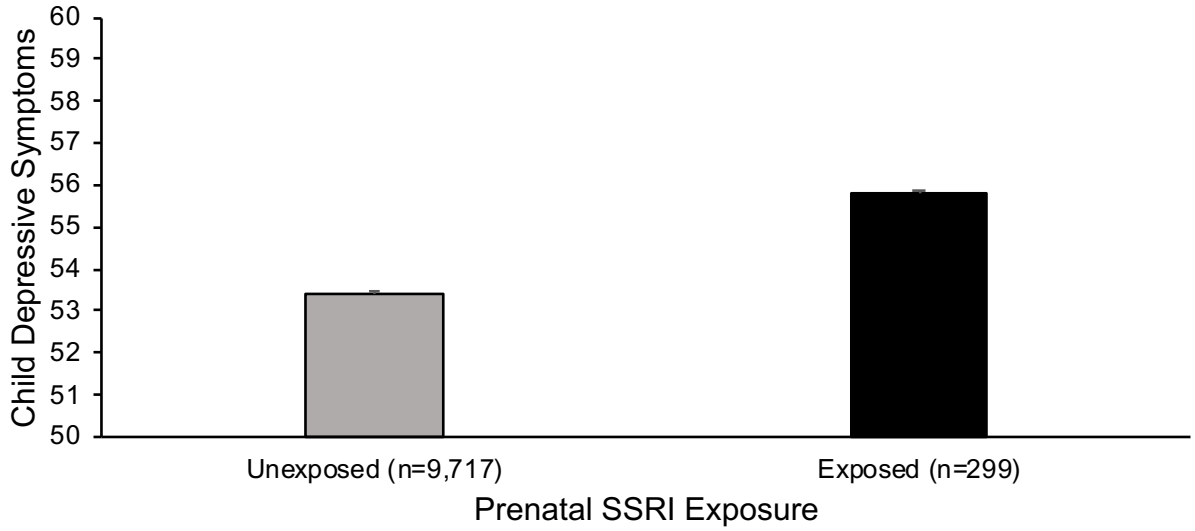

Figure 1. Mean current depressive symptoms in children exposed and unexposed prenatally to SSRIs.

3.2 Prenatal SSRI exposure and child brain outcomes

Prenatal SSRI exposure (i.e., before or after maternal knowledge of pregnancy, n=299 exposed, n=9,717 unexposed) was not associated with any brain structure outcome following correction for multiple testing (all p_{fdr} >0.12; **Tables 3-13**). The following nominally significant associations were observed between prenatal SSRI exposure and reduced subcortical brain

volumes: left caudate (b=-71.7; p=0.017), right hippocampus (b= -49.8; p=0.026), and left amygdala (b= -23.7, p=0.045). No associations between cortical thickness and prenatal SSRI exposure reached nominal levels of significance (all p_{fdr} >0.90, p>0.19). Subsequent *post-hoc* analyses conducted independent for exposure before maternal knowledge of pregnancy (n=274 exposed, 9,949 unexposed) and after maternal knowledge of pregnancy (n=212 exposed, n=10,155 unexposed) revealed no significant associations with subcortical volumes or cortical thickness after adjusting for multiple comparisons (all p_{fdr} >0.13). The following nominally significant associations were observed: prenatal SSRI exposure before and after maternal knowledge of pregnancy was nominally associated with reduced left amygdala volume (before: b= -26.6, p=0.032; after: b= -38.7, p=0.005) and SSRI exposure before maternal knowledge of pregnancy was associated with reduced right hippocampus (b= -57.2, p=0.014) and bilateral caudate volumes (left: b= -81.1, p=0.0099; right: b= -66.8, p=0.035).

3.3 Secondary Analyses

3.3.1 Maternal depression and child depression and brain structure

Lifetime presence of maternal depression and recent depressive symptoms (i.e., prior 6 months) were associated with increased child depressive symptoms (lifetime: b=2.15, t(df)=13.49(6,825), p=<2e-16; recent symptoms: b=0.38, t(df)=34.53(6,399), p=<2e-16; **Figure 2**).

However, there was no evidence that lifetime or recent maternal depression was associated with child brain structure (all p_{fdr} >0.29). The only nominally significant association to emerge from these analyses was that maternal lifetime depression was associated with decreased volume of the right putamen among children (b=-31.5, p=0.030). There were no nominally significant associations between recent maternal depressive symptoms and child brain structure (all ps >0.21).

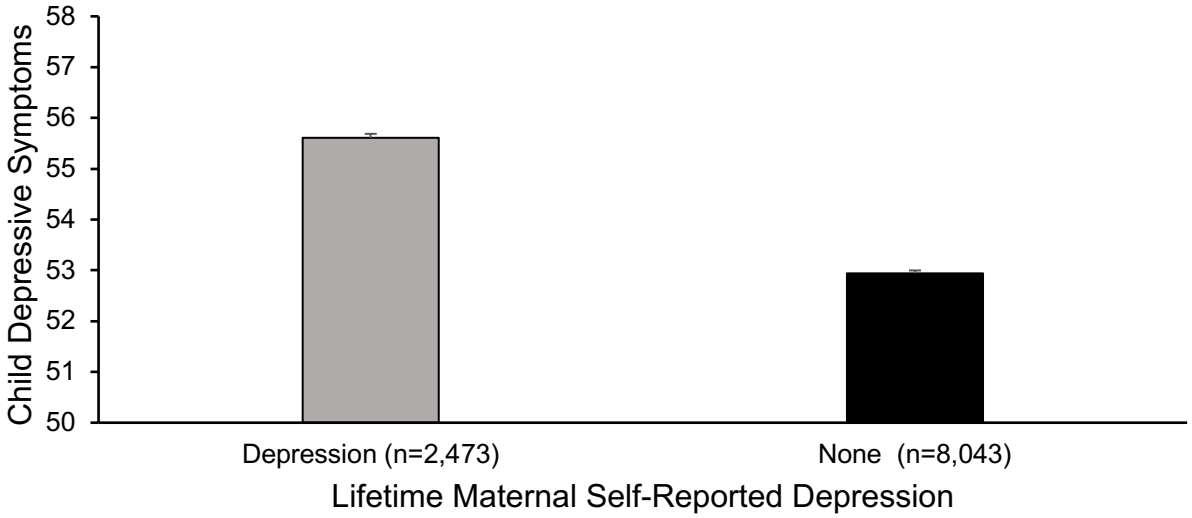

Figure 2. Mean current depressive symptoms in children with a maternal lifetime history of self-reported depression versus children whose mothers were not reported to have a lifetime history of depression.

3.3.2 Associations between child brain structure and depressive symptoms

Child depressive symptoms were not associated with child brain structure (all ps >0.10, all p_{fdr} >0.62).

Chapter 4: Discussion

The present study examined whether prenatal SSRI exposure is associated with child depression and brain structure (i.e., subcortical volume and cortical thickness). Two primary findings emerged. First, consistent with evidence from non-human animal models (Ansorge, Morelli, & Gingrich, 2008; Ansorge, Zhou, Lira, Hen, & Gingrich, 2004) and a limited human literature (Hanley et al., 2015; Hermansen et al., 2016; Lupattelli et al., 2018), but see also (Grzeskowiak et al., 2016; Misri et al., 2006; Nulman et al., 2012, 2015, 1997), we found that prenatal exposure to SSRIs is associated with increased child depression risk, even after accounting for maternal lifetime depression history. Second, prenatal SSRI exposure was not associated with individual differences in subcortical volumes or cortical thickness. Further, child brain structure was not related to child depressive symptoms. Collectively, these data suggest SSRI exposure may independently contribute to depression risk among children but not individual variability in gray matter brain structure, at least as measured by MRI. While depression during pregnancy is associated with a host of negative outcomes (e.g., cardiac malformations, poor neonatal adaptation; Fitton et al., 2019), these data suggest that SSRI use during pregnancy may also be associated with negative outcomes (e.g. depression risk to offspring).

Prior research on prenatal SSRI exposure and depression risk has produced equivocal results. One interesting theme to note in the prior literature is that the studies that have assessed children at later ages observed a positive association between prenatal SSRI exposure and depression (e.g., 15; (Liu et al., 2017; Malm et al., 2016)), while the majority of null association

findings have been conducted in younger children (e.g., <age 5; (Misri et al., 2006; Nulman et al., 1997); but see also: (Grzeskowiak et al., 2016; Nulman et al., 2012, 2015)). It is possible that null associations reported in the literature could be partially attributable to younger aged samples. This is consistent with non-human animal work suggesting that rodents exposed to SSRIs during the equivalence of the third trimester do not display abnormal emotional behavior during puphood but do display depressive-like behavior as adults (Ansorge et al., 2004). Thus, the positive results we obtained among children who were on average 10 years old may be partially attributable to children entering middle childhood, when depressive symptoms begin to be more commonly expressed. However, prior studies reporting that prenatal SSRI exposure is associated with depressive-like phenotypes in children as young 18 months (Brandlistuen et al., 2015) suggest that effects may be present earlier and that age alone cannot account for discrepant results in the literature.

It has long been speculated that SSRI exposure may influence brain structure development to increase risk for depression. Indeed, evidence from non-human animal models has shown that pregestational stress and prenatal stress, which are associated with depressive risk in offspring (Schmidt et al., 2018), increase serotonin signaling (Huang et al., 2012). Additionally, prenatal SSRIs decrease S100B, which mediates the positive outgrowth and survival of neurons, in human neonates at birth (Pawluski, Galea, Brain, Papsdorf, & Oberlander, 2009). As such, it is plausible that prenatal SSRI exposure may reduce neuronal survival and outgrowth through S100B. In contrast to these potential mechanisms, we find no evidence that prenatal SSRIs are associated with variability in child gray matter-related brain structure in specific ROIs at age 10. Together with evidence that variability in these brain structures were not associated with child depressive symptoms, these findings suggest that the impact of SSRIs may

be associated with depression via other mechanisms (e.g., structural connectivity, brain function, or finer grained brain structure).

Lastly, maternal depression history was associated with increased depressive symptoms among children. However, we found no significant associations between maternal history of depression and childhood brain metrics after correcting for multiple testing. Consistent with a prior report using this dataset, we do find nominal evidence that maternal history of depression is associated with reduced right putamen volume among kids (Pagliaccio, Alqueza, Marsh, & Auerbach, 2019). However, this nominally significant association in our sample would not survive correction for multiple testing in our study. It is possible that brain structure may be predictive of depressive symptoms that develop later in adolescence and that early onset depressive symptoms are less tied to brain structure.

4.1 Limitations and Future Directions

Several limitations regarding the current study are important to note. First, we do not have information on maternal depression during pregnancy. While observed relationships with prenatal SSRI exposure were independent of maternal lifetime depression history, we cannot exclude the possibility that depression during pregnancy specifically may be responsible for these. Relatedly, it is possible that prenatal SSRI exposure may be a proxy for more severe maternal depression. To confront these issues, after defending my master's thesis, I will examine whether these associations are present when considering child polygenic risk for depression. Nonetheless, we will be unable to fully disarticulate maternal depression during pregnancy and childhood from the impact of SSRI exposure.

Second, the analyzed dataset contained limited data on the timing of antidepressant exposure. While it was commendable to distinguish between exposure before or after knowledge of pregnancy given the thousands of other data points collected in the ABCD study, which was not designed to study prenatal exposure, the average point at which mothers knew they were pregnant in the sample was 6 weeks. Therefore, we cannot investigate differential effects of exposure with greater precision. Indeed, some evidence suggests that only SSRI exposure during late pregnancy (i.e., >29 weeks gestation) is associated with depression-related behavior among 5 year olds (Lupattelli et al., 2018). It is possible that prenatal SSRI exposure is only associated with child brain structure at precise exposure times. Third, the sample size of children exposed to SSRIs (n=299), while larger than most previous studies, was still small, especially given the variability in exposure timing and different types of SSRIs taken.

Fourth, we evaluated a priori brain regions based upon previous observations with depression. Given mounting evidence that clinical neuroscience may be plagued by false positives emerging from publication bias and underpowered heterogeneous patient samples, it is possible that priors from prior literature are misguiding. Before submitting this manuscript for publication, I will examine every brain region with correction for multiple testing. Further, it is possible that SSRIs might not impact gray matter metrics but may impact structural connectivity. Hence, after completing my master's thesis, I will examine DTI-derived brain metrics.

Finally, our brain and depression metrics were derived from one session when children were on average 10 years of age. It is possible that SSRI exposure is associated with brain structure during earlier development and/or brain structure trajectories and that such associations may partially account for its association with depression. As the ABCD study will follow recruited children for the next 10 years, future studies following future data releases will provide

the opportunity for longitudinal analyses as children enter the period of developmental risk for depression. This will allow us to examine the effects of prenatal SSRI exposure on brain structure throughout adolescence, a critical period for brain development and psychopathology risk.

4.2 Conclusions

In a study of 11,076 children with structural MRI data from the ABCD dataset, we find evidence that prenatal SSRI exposure is associated with increased depression risk during middle childhood that is independent of lifetime maternal depression. There was no evidence that child MRI-derived gray matter volume metrics (i.e. gray matter volume and cortical thickness across the whole brain and depression ROIs) may represent a mechanism underlying this association. Additional analyses will examine other imaging-derived metrics and whether observed associations between prenatal SSRI exposure and childhood depression remain when accounting for childhood polygenic risk for depression.

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Table 1. ABCD Sample Characteristics.

Variable (N)	No Prenatal SSRI Exposure (N=9,717)	Prenatal SSRI Exposure			Total (N=11,076)*
		Before Maternal Knowledge of Pregnancy (N=274)	After Maternal Knowledge of Pregnancy (N=212)	Total (N=299)	
Child Variables					
Age in years (11,076)	9.92 ± 0.62	9.94 ± 0.64	9.93 ± 0.63	9.94 ± 0.64	9.92 ± 0.62
Gender, female (11,071)	4,648 (47.8%)	125 (45.6%)	87 (41.0%)	133 (44.5%)	5300 (47.9%)
Birthweight in oz. (10,585)	112.62 ± 23.25	106.38 ± 25.57	105.47 ± 25.43	106.77 ± 25.21	112.16 ± 23.44
Race/Ethnicity (11,076)					
White	7,237 (74.5%)	265 (96.7%)	208 (98.1%)	288 (96.3%)	8285 (74.8%)
Black	2,037 (21.0%)	17 (6.2%)	13 (6.1%)	18 (6.0%)	2300 (20.8%)
Asian	571 (5.9%)	5 (1.8%)	6 (2.8%)	7 (2.3%)	678 (6.1%)
Pacific Islander	61 (0.6%)	0 (0%)	0 (0%)	0 (0%)	67 (0.6%)
Native American	304 (3.1%)	12 (4.4%)	8 (3.8%)	12 (4.0%)	369 (3.3%)
Hispanic	2,071 (21.3%)	23 (8.4%)	15 (7.1%)	26 (8.7%)	2254 (20.5%)
Other	658 (6.8%)	10 (3.7%)	6 (2.8%)	11 (3.7%)	731 (6.6%)
Pregnancy and Family Variables					
Planned Pregnancy (10,830)	5,971 (61.5%)	181 (66.1%)	149 (70.3%)	199 (66.6%)	6,634 (59.9%)
Prenatal Vitamin Use (10,627)	9,121 (93.9%)	260 (94.9%)	202 (95.3%)	285 (95.3%)	10,140 (91.6%)
Week Learned Pregnancy (9,794)	6.91 ± 6.76	7.30 ± 7.53	6.95 ± 7.24	7.09 ± 7.26	6.93 ± 6.80
Maternal Education: Years (10,326)	16.57 ± 2.78	17.57± 1.79	17.52 ± 1.86	17.57 ± 1.79	16.62 ± 2.75
Household Income (10,146)					
Less than $50k	2,658 (27.4%)	44 (16.1%)	31 (14.62%)	48 (16.1 %)	2,966 (26.8%)
$50k-$99,999k	2,503 (25.8%)	88 (32.1%)	58 (27.4%)	94 (31.4%)	2,894 (26.1%)
$100k or more	3,733 (38.4%)	128 (46.7%)	109 (51.4%)	141 (47.2%)	4286 (38.7%)
Maternal History of Dep (10,516)	1,980 (20.4%)	178 (65.0%)	130 (61.3%)	194 (64.9%)	2473 (22.3%)
Maternal Recent Dep Sxs (9,377)	53.73 ± 5.70	59.11± 7.73	58.73 ± 7.56	58.92 ± 7.64	54.01 ± 5.94
Prenatal Substance Exposure Before Knowing of Pregnancy					
SSRI (10,223)	0 (0%)	274 (100%)	187 (88.21%)	274 (91.64%)	274 (2.47%)
Alcohol (10,429)	2,280 (23.5%)	97 (35.4%)	69 (32.6%)	103 (34.5%)	2675 (24.2%)
Tobacco (10,813)	1,221 (12.6%)	36 (13.1%)	20 (9.4%)	39 (13.0%)	1478 (13.3%)
Cannabis (10,755)	492 (5.1%)	17 (6.2%)	8 (3.8%)	19 (6.4%)	622 (5.6%)
Prenatal Substance Exposure After Knowing of Pregnancy					
SSRI (10,367)	0 (0%)	187 (68.3%)	212 (100%)	212 (70.9%)	212 (1.9%)
Alcohol (10,798)	216 (2.2%)	8 (2.9%)	8 (3.8%)	8 (2.7%)	299 (2.7%)
Tobacco (10,828)	424 (4.4%)	11 (4.0%)	6 (2.8%)	11 (3.7%)	556 (5.0%)
Cannabis (10,813)	155 (1.6%)	6 (2.2%)	3 (1.4%)	7 (2.3%)	218 (2.0%)
Child Primary Outcomes of Interest					
Child Depression					
CBCL DSM-5 Depressive Sxs (11,068)	53.40 ± 5.56	55.77 ± 7.24	55.33 ± 7.22	55.78 ± 7.37	53.59 ± 5.73
Lifetime Depression Diagnosis (10,990)	485 (5.0%)	15 (5.8%)	9 (4.3%)	17 (5.7%)	550 (5.0%)
MDD Current	56 (0.6%)	0 (0%)	0 (0%)	0 (0%)	64 (0.6%)
MDD Partial Remission	25 (0.3%)	0 (0%)	0 (0%)	0 (0%)	25 (0.2%)
MDD Past	202 (2.1%)	10 (3.7%)	7 (3.3%)	11 (3.7%)	233 (2.1%)
PDD Current	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PDD Partial Remission	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PDD Past	5 (0.1%)	1 (0.4%)	0 (0%)	1 (0.3%)	7 (0.06%)
NOS Depression Current	22 (0.2%)	0 (0%)	0 (0%)	0 (0%)	24 (0.2%)
NOS Depression Past	214 (2.2%)	5 (1.8%)	2 (0.9%)	6 (2.0%)	241 (2.2%)
Gross Brain Structure (n= 9,712)					

Total Cortical Thickness	2.78 ± 0.10	2.80 ± 0.10	2.80 ± 0.10	2.80 ± 0.10	2.78 ± 0.10
ICV	1,514,371 ± 148,198.8	1,541,994.45 ± 157,763.03	1557733.12 ± 158429.90	1545964.84 ± 156157.22	1,513,468.71 ± 148,809.59
Subcortical Volumes (n=11,070)					
Amygdala (L)	1573.02 ± 229.54	1579.52 ± 234.13	1590.16 ± 234.51	1585.28 ± 233.51	1571.30 ± 229.61
Amygdala (R)	1615.92 ± 228.43	1621.83 ± 236.78	1633.21± 232.36	1626.51 ± 231.35	1613.65 ± 228.39
Caudate (L)	4011.80 ± 527.14	4021.67 ± 562.82	4081.44 ± 579.83	4030.18 ± 564.07	4008.59 ± 529.67
Caudate (R)	4162.21 ± 535.77	4175.02 ± 597.42	4239.59 ± 597.71	4186.83 ± 597.86	4159.10 ± 539.48
Hippocampus (L)	4042.94 ± 434.98	4088.76 ± 437.15	4119.11 ± 452.14	4100.94 ± 440.26	4041.24 ± 435.70
Hippocampus (R)	4094.74 ± 429.79	4116.60 ± 436.54	4159.19 ± 435.23	4129.56 ± 435.30	4090.71 ± 429.64
Nucleus Accumbens (L)	568.26 ± 115.15	571.97 ± 117.82	580.16 ± 112.81	570.95 ± 114.85	567.55 ± 115.13
Nucleus Accumbens (R)	617.66 ± 99.26	615.62 ± 96.18	621.67 ± 91.13	613.47 ± 94.49	616.46 ± 99.19
Putamen (L)	5955.33 ± 711.01	6031.99 ± 736.88	6066.49 ± 739.12	6045.87 ± 731.69	5950.89 ± 711.71
Putamen (R)	5790.91 ± 629.76	5868.95 ± 667.85	5893.31 ± 672.64	5881.64 ± 664.58	5787.38 ± 631.25
Cortical Thickness (n=11,070)					
Caudal Middle Frontal Cortex (L)	2.88 ± 0.15	2.88 ± 0.15	2.88 ± 0.14	2.88 ± 0.14	2.88 ± 0.15
Caudal Middle Frontal Cortex (R)	2.85 ± 0.15	2.84 ± 0.15	2.85 ± 0.15	2.84 ± 0.15	2.85 ± 0.15
Lateral OFC (L)	2.99 ± 0.15	3.00 ± 0.14	3.00 ± 0.14	3.00 ± 0.14	2.99 ± 0.15
Lateral OFC (R)	2.96 ± 0.16	2.98 ± 0.15	2.98 ± 0.15	2.98 ± 0.15	2.96 ± 0.16
Medial OFC (L)	2.73 ± 0.17	2.74 ± 0.17	2.74 ± 0.17	2.74 ± 0.17	2.73 ± 0.17
Medial OFC (R)	2.75 ± 0.18	2.77 ± 0.18	2.77 ± 0.17	2.77 ± 0.18	2.75 ± 0.18
Rostral ACC (L)	3.16 ± 0.21	3.18 ± 0.21	3.16 ± 0.20	3.18 ± 0.20	3.17 ± 0.21
Rostral ACC (R)	3.06 ± 0.22	3.07 ± 0.20	3.05 ± 0.20	3.06 ± 0.21	3.06 ± 0.22
Rostral Middle Frontal Cortex (L)	2.73 ± 0.15	2.75 ± 0.15	2.75 ± 0.15	2.75 ± 0.15	2.73 ± 0.15
Rostral Middle Frontal Cortex (R)	2.69 ± 0.15	2.70 ± 0.15	2.70 ± 0.15	2.70 ± 0.15	2.69 ± 0.15
Superior Frontal Cortex (L)	3.14 ± 0.15	3.14 ± 0.15	3.15 ± 0.15	3.15 ± 0.15	3.14 ± 0.15
Superior Frontal Cortex (R)	3.10 ± 0.15	3.10 ± 0.14	3.10 ± 0.14	3.10 ± 0.14	3.10 ± 0.15

Notes: Dep = Depression; Sxs = Symptoms; SSRI = Selective Serotonin Reuptake Inhibitor; CBCL = Child Behavior Checklist; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; MDD = Major Depressive Disorder; PDD = Persistent Depressive Disorder; NOS = Not Otherwise Specified (i.e. Unspecified); ICV = intracranial volume; L = left; R = right; OFC = orbitofrontal cortex; ACC = anterior cingulate cortex; * Some participants with acceptable MRI data did not have data for prenatal SSRI exposure. Therefore, the column totals do not add up to 11,076. Values are either N(%) or mean ± standard deviation. Units for subcortical volumes are mm^3 and for cortical thickness are mm.

Table 2. Prenatal SSRI Exposure and Child Depressive Symptoms: Full Regression Results

N= 7,403	**Child Depressive Symptoms**	
Variable	b	*p*
Variable of Interest		
Prenatal SSRI Exposure	0.9516	0.010585
Pregnancy and Family Variables		
Planned Pregnancy	-0.2559	0.095073
Prenatal Vitamin Use	-0.3.532	0.301420
Week Learned Pregnancy	6.802e-03	0.495693
Maternal Education: Years	-2.249e-04	0.994555
Household Income		
$50k-$99,999	-0.8883	8.74e-06
$100k or more	-1.447	7.40e-11
Prenatal Exposure Before Maternal Knowledge		
Alcohol	0.2563	0.119135
Tobacco	0.5309	0.037145
Cannabis	0.04981	0.889545
Prenatal Exposure After Maternal Knowledge		
Alcohol	0.9060	0.046550
Tobacco	-0.07660	0.850914
Cannabis	0.5319	0.415376
Maternal History of Depression	2.185	< 2e-16
Child Variables		
Age	0.01940	0.022847
Sex	0.7658	3.23e-09
Birthweight	-2.975e-03	0.382417
Race and Ethnicity		
White	0.9415	0.000129
Black	-0.2731	0.279889
Asian	0.2027	0.501435
Pacific Islander	-1.093	0.203159
Native American	0.7146	0.069327
Other Race	0.8798	0.008690
Hispanic	-0.2685	0.203287

Table 3. Prenatal SSRI Exposure and Child Amygdala Volume: Full Regression Results

N = 7,399	**Amygdala**			
	Left		Right	
Variable	b	*p*	b	*p*
Variable of Interest				
Prenatal SSRI Exposure	-23.71	0.0451	-17.91	0.1263
Pregnancy and Family Variables				
Planned Pregnancy	2.387	0.6250	-6.832	0.1580
Prenatal Vitamin Use	-5.213	0.6316	27.45	0.0108
Week Learned Pregnancy	0.3415	0.2825	0.4318	0.1702
Maternal Education: Years	2.006	0.0570	1.513	0.1470
Household Income				
$50k-$99,999	3.692	0.5618	5.162	0.4125
$100k or more	5.468	0.4404	9.182	0.1908
Prenatal Exposure Before Maternal Knowledge				
Alcohol	3.862	0.4612	-0.9170	0.8598
Tobacco	-8.089	0.3185	-13.79	0.0859
Cannabis	11.56	0.3110	18.20	0.1073
Prenatal Exposure After Maternal Knowledge				
Alcohol	1.358	0.9254	19.67	0.1709
Tobacco	-5.283	0.6837	-15.51	0.2272
Cannabis	1.120	0.9570	10.38	0.6142
Maternal History of Depression	-6.672	0.1980	-1.271	0.8043
Child Variables				
Age	0.5382	0.0486	0.03871	0.8864
Sex	54.99	< 2e-16	49.60	< 2e-16
Birthweight	-0.06115	0.5788	-0.1028	0.3465
Race and Ethnicity				
White	1.487	0.8500	-1.479	0.8494
Black	-46.15	1.25e-08	-34.44	1.77e-05
Asian	-3.008	0.7559	-7.670	0.4234
Pacific Islander	-36.57	0.1803	-32.19	0.2332
Native American	23.84	0.0585	28.66	0.0216
Other Race	-2.654	0.8039	-12.61	0.2338
Hispanic	3.675	0.5957	10.27	0.1345

Table 4. Prenatal SSRI Exposure and Child Caudate Volume: Full Regression Results

N=7,399	**Caudate**			
	Left		Right	
Variable	b	*p*	b	*p*
Variable of Interest				
Prenatal SSRI Exposure	-71.74	0.01727	-53.18	0.080238
Pregnancy and Family Variables				
Planned Pregnancy	-7.593	0.53552	13.01	0.294582
Prenatal Vitamin Use	-25.24	0.35738	-26.18	0.345255
Week Learned Pregnancy	0.5472	0.49378	0.4155	0.607730
Maternal Education: Years	7.939	0.00310	9.276	0.000615
Household Income				
$50k-$99,999	29.45	0.06954	13.92	0.394782
$100k or more	3.964	0.82622	-0.8282	0.963733
Prenatal Exposure Before Maternal Knowledge				
Alcohol	-15.88	0.23178	-14.59	0.276702
Tobacco	-1.773	0.93121	6.232	0.763901
Cannabis	-9.233	0.74850	-16.95	0.560488
Prenatal Exposure After Maternal Knowledge				
Alcohol	-24.72	0.49848	-36.70	0.320498
Tobacco	-27.67	0.39892	-41.81	0.207344
Cannabis	55.82	0.28592	55.20	0.296953
Maternal History of Depression	-1.210	0.92662	-3.570	0.787919
Child Variables				
Age	-1.959	0.00316	-2.313	0.000653
Sex	-67.08	7.58e-09	-78.17	3.49e-11
Birthweight	0.6194	0.02495	0.5443	0.051886
Race and Ethnicity				
White	42.68	0.03179	41.63	0.038328
Black	13.13	0.52411	33.27	0.109816
Asian	-41.35	0.09207	-47.31	0.056427
Pacific Islander	75.95	0.27723	-16.10	0.387386
Native American	-14.27	0.65500	60.92	0.617851
Other Race	-6.837	0.79910	1.479	0.956642
Hispanic	-14.44	0.41115	-19.10	0.282564

Table 5. Prenatal SSRI Exposure and Child Hippocampus Volume: Full Regression Results

N= 7,399	**Hippocampus**			
	Left		Right	
Variable	b	*p*	b	*p*
Variable of Interest				
Prenatal SSRI Exposure	-22.30	0.343625	-49.77	0.025629
Pregnancy and Family Variables				
Planned Pregnancy	-4.814	0.618316	6.297	0.490645
Prenatal Vitamin Use	32.11	0.136422	39.57	0.052385
Week Learned Pregnancy	-0.03025	0.961666	0.6449	0.278737
Maternal Education: Years	3.551	0.089096	2.195	0.267138
Household Income				
$50k-$99,999	25.13	0.046679	25.01	0.036633
$100k or more	34.31	0.014548	30.14	0.023436
Prenatal Exposure Before Maternal Knowledge				
Alcohol	-9.049	0.383587	6.422	0.513596
Tobacco	-10.81	0.501876	-3.632	0.811554
Cannabis	37.00	0.102022	40.25	0.060091
Prenatal Exposure After Maternal Knowledge				
Alcohol	-0.3405	0.990540	6.205	0.819276
Tobacco	-4.536	0.860156	-41.23	0.090629
Cannabis	-15.78	0.701483	-40.28	0.300931
Maternal History of Depression	-9.357	0.363087	-7.336	0.451237
Child Variables				
Age	0.6833	0.200343	0.5701	0.256823
Sex	32.21	0.000434	29.52	0.000643
Birthweight	-0.1739	0.424059	-0.04951	0.809791
Race and Ethnicity				
White	9.935	0.523282	10.21	0.488152
Black	-70.30	1.13e-05	-79.86	1.41e-07
Asian	-7.947	0.676822	14.46	0.423113
Pacific Islander	-17.99	0.741190	-75.20	0.145266
Native American	-17.34	0.485203	-23.28	0.322576
Other Race	-13.01	0.537869	-4.190	0.833865
Hispanic	-14.45	0.278322	14.88	0.239560

Table 6. Prenatal SSRI Exposure and Child Nucleus Accumbens Volume: Full Regression Results

N=7,399	**Nucleus Accumbens**			
	Left		Right	
Variable	b	*p*	b	*p*
Variable of Interest				
Prenatal SSRI Exposure	-0.1038	0.98672	-8.422	0.12814
Pregnancy and Family Variables				
Planned Pregnancy	-1.992	0.44030	4.771	0.03662
Prenatal Vitamin Use	-0.8652	0.88021	2.172	0.66903
Week Learned Pregnancy	-0.1623	0.33355	-0.08096	0.58568
Maternal Education: Years	-0.2037	0.71396	-0.1392	0.77768
Household Income				
$50k-$99,999	2.783	0.40682	4.339	0.14494
$100k or more	0.6966	0.85217	3.805	0.25120
Prenatal Exposure Before Maternal Knowledge				
Alcohol	-1.565	0.57149	-2.461	0.31540
Tobacco	-5.142	0.22943	-6.077	0.10903
Cannabis	-3.905	0.51703	5.672	0.28766
Prenatal Exposure After Maternal Knowledge				
Alcohol	-4.433	0.56288	3.697	0.58532
Tobacco	-3.768	0.58180	-3.015	0.61904
Cannabis	0.5941	0.95684	-5.432	0.57589
Maternal History of Depression	-0.4744	0.86225	-1.655	0.49473
Child Variables				
Age	-0.4686	0.00123	-0.7657	1.87e-09
Sex	1.108	0.65327	3.603	0.09803
Birthweight	0.2982	3.12e-07	0.2961	9.25e-09
Race and Ethnicity				
White	-7.802	0.06020	-4.651	0.20583
Black	-6.195	0.14699	0.3097	0.93485
Asian	-5.941	0.24475	-7.039	0.11987
Pacific Islander	-24.06	0.09382	-24.16	0.05869
Native American	0.4475	0.94635	-3.867	0.51178
Other Race	-2.284	0.68610	-2.672	0.59278
Hispanic	-1.342	0.71391	-1.648	0.61128

Table 7. Prenatal SSRI Exposure and Child Putamen Volume: Full Regression Results

N = 7,399	**Putamen**			
	Left		Right	
Variable	b	*p*	b	*p*
Variable of Interest				
Prenatal SSRI Exposure	-18.17	0.64984	21.17	0.5396
Pregnancy and Family Variables				
Planned Pregnancy	24.97	0.12770	23.40	0.0962
Prenatal Vitamin Use	33.13	0.36525	36.59	0.2445
Week Learned Pregnancy	0.3896	0.71532	-0.1688	0.8540
Maternal Education: Years	-1.282	0.71878	-1.933	0.5294
Household Income				
$50k-$99,999	46.50	0.03070	25.86	0.1639
$100k or more	33.16	0.16604	20.80	0.3144
Prenatal Exposure Before Maternal Knowledge				
Alcohol	-5.788	0.74318	-5.880	0.6992
Tobacco	32.34	0.23703	39.70	0.0917
Cannabis	12.49	0.74499	2.871	0.9307
Prenatal Exposure After Maternal Knowledge				
Alcohol	88.89	0.06813	53.06	0.2052
Tobacco	10.90	0.80316	-8.576	0.8196
Cannabis	46.80	0.50282	90.02	0.1335
Maternal History of Depression	-16.26	0.35234	-30.67	0.0416
Child Variables				
Age	-2.502	0.00547	-3.464	6.02e-06
Sex	120.8	9.14e-15	143.4	< 2e-16
Birthweight	-0.1993	0.58955	-0.2123	0.5030
Race and Ethnicity				
White	26.83	0.31074	17.37	0.4460
Black	-44.09	0.10653	-71.69	0.0024
Asian	95.02	0.00352	114.5	4.76e-05
Pacific Islander	26.55	0.77464	-22.94	0.7744
Native American	-75.78	0.07399	-39.52	0.2802
Other Race	12.44	0.72873	70.56	0.0221
Hispanic	-8.999	0.69712	13.88	0.4909

Table 8. Prenatal SSRI Exposure and Child Caudal Middle Frontal Gyrus Cortical Thickness: Full Regression Results

N = 7,399	**Caudal Middle Frontal Gyrus**			
	Left		Right	
Variable	b	*p*	b	*p*
Variable of Interest				
Prenatal SSRI Exposure	5.630e-03	0.555016	-2.341e-03	0.80924
Pregnancy and Family Variables				
Planned Pregnancy	-6.178e-03	0.117393	-6.396e-03	0.11087
Prenatal Vitamin Use	0.01214	0.166606	2.396e-04	0.97857
Week Learned Pregnancy	1.212e-04	0.636611	4.569e-04	0.07991
Maternal Education: Years	2.671e-04	0.753154	-4.120e-04	0.63328
Household Income				
$50k-$99,999	7.840e-03	0.126384	0.01374	0.00844
$100k or more	4.794e-03	0.401506	0.01158	0.04624
Prenatal Exposure Before Maternal Knowledge				
Alcohol	-5.571e-03	0.187714	-0.01127	0.00877
Tobacco	-2.952e-03	0.651823	-5.374e-03	0.41900
Cannabis	-8.221e-03	0.372199	-5.641e-04	0.95198
Prenatal Exposure After Maternal Knowledge				
Alcohol	0.01373	0.240863	0.02910	0.01455
Tobacco	-5.464e-04	0.958343	0.01090	0.30528
Cannabis	9.973e-03	0.552278	-0.01690	0.32196
Family History of Depression	3.807e-04	0.927445	-3.839e-03	0.36635
Child Variables				
Age	-4.815e-04	0.029596	-4.245e-04	0.05942
Sex	-0.02795	1.34e-13	-0.03661	< 2e-16
Birthweight	4.438e-05	0.617994	1.927e-04	0.03327
Race and Ethnicity				
White	8.974e-03	0.157286	6.825e-03	0.29007
Black	0.01159	0.075888	8.743e-03	0.18773
Asian	-0.01383	0.076355	-0.01265	0.11078
Pacific Islander	-9.884e-03	0.652736	-0.04433	0.04710
Native American	-5.694e-03	0.575275	-0.01781	0.08476
Other Race	-8.285e-04	0.923555	-0.01094	0.21261
Hispanic	-0.02452	1.13e-05	-6.995e-03	0.21786

Table 9. Prenatal SSRI Exposure and Child Rostral Middle Frontal Gyrus Cortical Thickness: Full Regression Results

N= 7,399	**Rostral Middle Frontal Gyrus**			
	Left		Right	
Variable	b	*p*	b	*p*
Variable of Interest				
Prenatal SSRI Exposure	2.187e-03	0.806278	6.736e-03	0.45498
Pregnancy and Family Variables				
Planned Pregnancy	-3.986e-03	0.278974	-2.666e-03	0.47337
Prenatal Vitamin Use	5.214e-03	0.524532	2.256e-03	0.78520
Week Learned Pregnancy	2.370e-04	0.322413	1.767e-04	0.46525
Maternal Education: Years	1.468e-03	0.064512	1.515e-03	0.05926
Household Income				
$50k-$99,999	4.465e-03	0.351760	4.130e-03	0.39434
$100k or more	3.518e-03	0.510191	1.239e-03	0.81862
Prenatal Exposure Before Maternal Knowledge				
Alcohol	-1.738e-03	0.659970	-4.340e-03	0.27698
Tobacco	5.954e-04	0.922385	-6.142e-03	0.31997
Cannabis	-1.144e-03	0.894137	-1.085e-03	0.90065
Prenatal Exposure After Maternal Knowledge				
Alcohol	0.02343	0.032073	0.01955	0.07655
Tobacco	-7.365e-03	0.451020	7.507e-03	0.44721
Cannabis	0.01093	0.485211	-0.01105	0.48499
Maternal History of Depression	2.424e-03	0.534838	-8.922e-04	0.82120
Child Variables				
Age	-1.911e-03	< 2e-16	-1.749e-03	< 2e-16
Sex	7.312e-03	0.037546	6.418e-03	0.07053
Birthweight	-3.822e-05	0.645342	-6.209e-05	0.45915
Race and Ethnicity				
White	9.454e-03	0.110683	0.01077	0.07225
Black	-0.01758	0.004001	-0.01930	0.00178
Asian	-4.200e-03	0.564767	-3.198e-03	0.66439
Pacific Islander	-8.668e-03	0.673372	-0.02938	0.15805
Native American	4.719e-03	0.619353	-2.347e-03	0.80686
Other Race	2.230e-03	0.782009	4.283e-03	0.59875
Hispanic	-0.01875	0.000337	-0.01567	0.00302

Table 10. Prenatal SSRI Exposure and Child Lateral OFC Cortical Thickness: Full Regression Results

N= 7,399	**Lateral OFC**			
	Left		Right	
Variable	b	*p*	b	*p*
Variable of Interest				
Prenatal SSRI Exposure	-0.01284	0.19386	-8.434e-03	0.400181
Pregnancy and Family Variables				
Planned Pregnancy	-3.163e-03	0.43943	1.368e-03	0.742450
Prenatal Vitamin Use	5.624e-03	0.53654	0.01377	0.136727
Week Learned Pregnancy	-1.251e-04	0.63801	9.480e-05	0.726015
Maternal Education: Years	1.089e-03	0.21594	1.498e-03	0.093554
Household Income				
$50k-$99,999	0.01113	0.03622	0.01090	0.043293
$100k or more	0.01299	0.02823	0.01232	0.040300
Prenatal Exposure Before Maternal Knowledge				
Alcohol	1.768e-03	0.68654	-5.060e-04	0.909515
Tobacco	-2.611e-03	0.70014	-6.471e-03	0.347355
Cannabis	-3.889e-03	0.68383	-2.442e-03	0.801518
Prenatal Exposure After Maternal Knowledge				
Alcohol	0.01287	0.28923	-5.248e-03	0.671115
Tobacco	-3.398e-03	0.75393	3.041e-03	0.782406
Cannabis	0.01560	0.36987	0.01875	0.289694
Maternal History of Depression	4.885e-03	0.25956	2.479e-03	0.573243
Child Variables				
Age	-2.481e-03	< 2e-16	-2.344e-03	< 2e-16
Sex	0.01043	0.00758	6.594e-03	0.097753
Birthweight	-2.827e-04	0.00219	-2.558e-04	0.006467
Race and Ethnicity				
White	0.02676	4.75e-05	0.02460	0.000234
Black	-0.01607	0.01746	-0.02358	0.000593
Asian	-0.01156	0.15250	-7.414e-03	0.366620
Pacific Islander	-0.03285	0.14869	-0.03519	0.126003
Native American	9.702e-04	0.92655	2.414e-03	0.821408
Other Race	0.02235	0.01257	0.02253	0.013430
Hispanic	-6.330e-03	0.27212	-0.01632	0.005413

Table 11. Prenatal SSRI Exposure and Child Medial OFC Cortical Thickness: Full Regression Results

N= 7,399	**Medial OFC**			
	Left		Right	
Variable	b	*p*	b	*p*
Variable of Interest				
Prenatal SSRI Exposure	5.630e-03	0.555016	7.235e-03	0.51023
Pregnancy and Family Variables				
Planned Pregnancy	-6.178e-03	0.117393	-1.567e-03	0.73098
Prenatal Vitamin Use	0.01214	0.166606	0.02779	0.00609
Week Learned Pregnancy	1.212e-04	0.636611	-2.032e-04	0.49263
Maternal Education: Years	2.671e-04	0.753154	1.610e-03	0.10016
Household Income				
$50k-$99,999	7.840e-03	0.126384	8.607e-03	0.14520
$100k or more	4.794e-03	0.401506	6.227e-03	0.34432
Prenatal Exposure Before Maternal Knowledge				
Alcohol	-5.571e-03	0.187714	-1.216e-03	0.80314
Tobacco	-2.952e-03	0.651823	-6.625e-03	0.37975
Cannabis	-8.221e-03	0.372199	5.161e-03	0.62742
Prenatal Exposure After Maternal Knowledge				
Alcohol	0.01373	0.240863	0.01730	0.20093
Tobacco	-5.464e-04	0.958343	0.01553	0.19778
Cannabis	9.973e-03	0.552278	9.261e-03	0.63267
Maternal History of Depression	3.807e-04	0.927445	1.099e-03	0.81972
Child Variables				
Age	-4.815e-04	0.029596	-2.745e-03	< 2e-16
Sex	-0.02795	1.34e-13	0.01393	0.00139
Birthweight	4.438e-05	0.617994	-5.750e-04	2.29e-08
Race and Ethnicity				
White	8.974e-03	0.157286	6.930e-03	0.34371
Black	0.01159	0.075888	-0.01415	0.06004
Asian	-0.01383	0.076355	7.890e-03	0.38054
Pacific Islander	-9.884e-03	0.652736	-0.04675	0.06408
Native American	-5.694e-03	0.575275	0.01392	0.23498
Other Race	-8.285e-04	0.923555	-4.205e-03	0.67325
Hispanic	-0.02452	1.13e-05	1.427e-03	0.82444

Table 12. Prenatal SSRI Exposure and Child Rostral ACC Cortical Thickness: Full Regression Results

N=7,399	**Rostral ACC**			
	Left		Right	
Variable	b	*p*	b	*p*
Variable of Interest				
Prenatal SSRI Exposure	-0.01059	0.415030	-0.01051	0.4430
Pregnancy and Family Variables				
Planned Pregnancy	-4.879e-03	0.366047	-4.573e-03	0.4210
Prenatal Vitamin Use	8.845e-04	0.941215	2.865e-03	0.8206
Week Learned Pregnancy	-2.173e-04	0.535559	9.998e-05	0.7866
Maternal Education: Years	1.098e-03	0.343205	2.371e-03	0.0522
Household Income				
$50k-$99,999	2.033e-04	0.976782	-1.638e-03	0.8240
$100k or more	-2.372e-03	0.760624	-9.679e-03	0.2385
Prenatal Exposure Before Maternal Knowledge				
Alcohol	4.787e-03	0.406829	-1.166e-03	0.8480
Tobacco	-5.947e-03	0.505168	2.586e-03	0.7834
Cannabis	-0.01200	0.340421	-5.550e-03	0.6756
Prenatal Exposure After Maternal Knowledge				
Alcohol	0.01780	0.266691	-5.370e-03	0.7502
Tobacco	0.01472	0.302232	-0.01784	0.2358
Cannabis	0.02989	0.192844	-0.03064	0.2049
Maternal History of Depression	3.500e-03	0.539409	5.844e-03	0.3310
Child Variables				
Age	-2.712e-03	< 2e-16	-2.233e-03	3.41e-12
Sex	-0.01728	0.000824	1.312e-03	0.8091
Birthweight	-4.555e-04	0.000185	-2.267e-04	0.0770
Race and Ethnicity				
White	0.02940	0.000694	0.01916	0.0359
Black	0.01727	0.052186	-0.01142	0.2235
Asian	-0.02350	0.027376	-8.366e-03	0.4558
Pacific Islander	-0.01191	0.689074	-0.01262	0.6885
Native American	-1.706e-05	0.999018	0.01425	0.3295
Other Race	0.01149	0.330942	0.02171	0.0809
Hispanic	-0.01889	0.013174	-0.01042	0.1938

Table 13. Prenatal SSRI Exposure and Child Superior Frontal Gyrus Cortical Thickness: Full Regression Results

N= 7,339	**Superior Frontal Gyrus**			
	Left		Right	
Variable	b	*p*	b	*p*
Variable of Interest				
Prenatal SSRI Exposure	1.125e-03	0.90382	3.764e-04	0.9677
Pregnancy and Family Variables				
Planned Pregnancy	-3.411e-03	0.37343	-1.883e-04	0.9607
Prenatal Vitamin Use	7.490e-03	0.38034	9.748e-03	0.2525
Week Learned Pregnancy	1.312e-04	0.59888	1.216e-04	0.6251
Maternal Education: Years	1.109e-03	0.18126	1.407e-03	0.0889
Household Income				
$50k-$99,999	7.712e-03	0.12374	8.156e-03	0.1025
$100k or more	5.971e-03	0.28459	5.149e-03	0.3547
Prenatal Exposure Before Maternal Knowledge				
Alcohol	-4.706e-03	0.25351	-2.615e-03	0.5246
Tobacco	-1.365e-03	0.83045	-4.920e-03	0.4390
Cannabis	7.654e-04	0.93194	-6.838e-04	0.9390
Prenatal Exposure After Maternal Knowledge				
Alcohol	0.02746	0.01583	0.02643	0.0199
Tobacco	-3.792e-03	0.70987	5.193e-03	0.6095
Cannabis	3.274e-03	0.84092	-7.656e-03	0.6380
Maternal History of Depression	-2.175e-03	0.59358	4.187e-04	0.9179
Child Variables				
Age	-1.344e-03	2.81e-10	-1.192e-03	2.16e-08
Sex	-0.01507	3.73e-05	-0.01449	7.10e-05
Birthweight	-2.411e-04	0.00529	-1.576e-04	0.0678
Race and Ethnicity				
White	9.487e-03	0.12474	6.436e-03	0.2964
Black	5.012e-03	0.43180	-2.780e-03	0.6619
Asian	-0.01010	0.18433	-4.586e-03	0.5457
Pacific Islander	-0.01980	0.35778	-0.02760	0.1983
Native American	-4.375e-03	0.65890	-5.639e-03	0.5683
Other Race	1.522e-03	0.85606	1.605e-03	0.8479
Hispanic	-0.01440	0.00835	-0.01126	0.0384