Maternal Perinatal Depressive Symptoms, Prenatal Maternal Selective Serotonin Reuptake Inhibitor Antidepressants, and Executive Functions in Children: A 12-Year Longitudinal Study

Sarah M. Hutchison, PhD*, Ursula Brain, BA*, Ruth E. Grunau, PhD*, Adele Diamond, PhD†, Tim F. Oberlander, MD, FRPC*,‡

ABSTRACT

Objective: To determine whether mothers' depressive symptoms with or without exposure to selective serotonin reuptake inhibitor (SSRI) antidepressant treatments during pregnancy were associated with executive functions (EFs) in offspring at 6 and 12 years of age.

Methods: A prospective cohort of 191 mothers and their children participated in the study. Clinician-rated reports of mothers' depressive symptoms were obtained spanning the third trimester during pregnancy to 12 years later. Children's EFs were measured using 2 computer-based tasks (Flanker/Reverse Flanker, Hearts and Flowers [HF]) and mothers' reports of EFs using the Behavior Rating Inventory of Executive Function (BRIEF) when the child was 6 and 12 years old.

Results: Longitudinal analyses showed that all children were both faster and more accurate on both Flanker/Reverse Flanker and HF with age. Fewer maternal prenatal depressive symptoms were associated with better accuracy on HF in children at 6 years of age and better EF skills as measured by the BRIEF at 6 and 12 years. Mothers' ratings of their children at 12 years indicated more executive dysfunction in children with prenatal SSRI exposure than for children without prenatal SSRI exposure, but this was no longer significant once prenatal depressive symptoms were taken into account.

Conclusion: Prenatal and later depressive symptoms, not prenatal SSRI exposure, seems to affect offspring that continues into preadolescence, highlighting the importance of long-term mental health follow-up in mothers to ensure optimal development of children's EFs and hence their optimal development in school, in social relations, and in life generally.

Index terms: child cognitive development, depression, pharmacology, neuropsychology, SSRI

Executive functions (EFs), which are higher-order cognitive processes that depend on prefrontal cortex and other neural regions with which it is interconnected, include working memory, inhibitory control (attention regulation and self-control), and cognitive flexibility.[1,2] EFs are particularly sensitive to early life environments.[3] Individuals with better EFs are more likely to have better academic, social, and professional success, in addition to better overall mental and physical health.[4] One important part of early life environments is the mental health of mothers. A meta-analysis of 16 studies showed that perinatal maternal depression was significantly associated with poorer child EFs.[5] The perinatal period ranges from conception to the end of the first postpartum year[6] and the prenatal period ranges from conception to delivery. Prenatal depressive symptoms may alter fetal development in a variety of ways including epigenetic changes[7] and postnatal depressive symptoms may negatively affect the parent-child relationship over time[8] as well as the child's cognitive abilities.[9]

In addition to the impact of depressive symptoms on the development of EFs, there are also concerns about the use of medications to treat these symptoms. Selective serotonin reuptake inhibitor (SSRI) antidepressants are the most common form of pharmacotherapy to treat and prevent depressive symptoms. They putatively work by altering central nervous system levels of the neurotransmitter serotonin.[10] Serotonin and its multiple receptors play important roles in influencing complex cognition, such as EFs.[11] Increasing clinical evidence suggests that prenatal exposure to SSRIs may have a negative impact on infant neurodevelopment, with long-lasting consequences on emotional and cognitive development into childhood.[12–14] One exception was a study of 5- and 6-year-olds, which failed to find significant differences in performance on an EF task between children with either: (1) prenatal SSRI exposure, (2) medically untreated

* Department of Pediatrics, University of British Columbia and BC Children's Hospital Research Institute, Vancouver, BC, Canada; † Developmental Cognitive Neuroscience Lab, Psychiatry, University of British Columbia and BC Children's Hospital Research Institute, Vancouver, BC, Canada; and ‡ School of Population and Public Health, University of British Columbia and BC Children's Hospital Research Institute, Vancouver, BC, Canada.

Received: 15 January 2025 / Accepted: 30 October 2025
Available online 24 December 2025

This research was funded by the Canadian Institutes of Health Research (CIHR) Grants MOP 54490, 57837, 86296 (T.F. Oberlander). S.M. Hutchison was supported by postdoctoral fellowships from the BC Children's Hospital Research Institute (BCCHRI), Brain Canada, and Kids Brain Health Network. R.E. Grunau is supported by a senior scientist salary award from BCCHRI. A. Diamond is supported by a Canada Research Chair Tier 1 (CRC #950-27472) from the Canada Excellence Research Chairs Program. T.F. Oberlander is the R. Howard Webster Professor in Brain Imaging and Child Development. Funding sources had no role in the study.

Disclosure: The authors declare no conflict of interest.

Contact information: Sarah M. Hutchison, PhD, Department of Pediatrics, University of British Columbia, BC Children's Hospital Research Institute, Vancouver, BC V6H 3V4, Canada; e-mail: shutchison@bcchr.ca.

Journal of Developmental & Behavioral Pediatrics (2025) 00:00
http://dx.doi.org/10.1097/DBP.0000000000001440

perinatal depression exposure, or (3) no exposure to SSRI or perinatal depression.[15]

The above references used performance-based measures of EFs. Behavior rating scales (e.g., parent, teacher or self-reports) have also been used to measure EF skills within everyday family, school, or community settings.[16] A population-based study with over 4000 participants, that used EFs rating scales, reported that preschoolers exposed to SSRIs were more likely to have poorer overall EFs even when depressive symptoms when children were 2 months old or 3 years old were controlled for.[17] However, this association was no longer significant once depressive symptoms during pregnancy were taken into account. In another study, 20 women treated with antidepressants during pregnancy reported levels of overall EFs in their 4-year-olds similar to that of 21 matched controls who were not depressed or treated with antidepressant medication.[18] However, this study did not include direct measures of maternal depressive symptoms. Thus, the impact of maternal mood is not known. In a cohort of 139 children aged 6 years, we have previously reported that there were no significant differences between mothers with and without SSRI treatment who reported on their children's overall EFs.[19] In addition, higher levels of maternal depressive symptoms, especially when their children were 3 years old, were associated with poorer reports of EF skills when children were 6 years old. In sum, these studies suggest the importance of controlling for maternal depressive symptoms to reduce confounding by indication that the possible impact of SSRI exposure may be because of the underlying condition that led to the treatment and not the treatment itself.

The present study was undertaken to examine the possible impact of prenatal SSRI exposure and maternal depressive symptoms on children's EFs over 12 years using both performance-based EF measures and ratings completed by the mother. As previous research on this topic has been limited to preschoolers and young children, following the same cohort of children with and without prenatal SSRI exposure from in utero to preadolescence addresses a significant gap in the literature. Based on previous research, we expected that children would improve on performance-based measures of EFs with age.[20,21] We also expected that a different pattern of results would emerge for performance-based measures and rating scales of EFs, as they are typically not highly correlated and may assess different underlying mental constructs.[22] No specific predictions on performance-based measures of EFs were made because this is the first study to assess the impact of prenatal SSRI exposure on children's EFs over 12 years. In clinical settings, the Behavior Rating Inventory of Executive Function (BRIEF) may be useful to identify children with behavioural problems who may be at risk for the development of school and social problems.[23] As this was the first study to examine longitudinal maternal reports of EFs, maternal depressive symptoms, and prenatal SSRI exposure over 12 years, no predictions were made on how these associations might change over time.

METHODS

Participants

Pregnant women were recruited from the community and clinics during the second trimester of pregnancy for a longitudinal cohort study. Ethical approval for the study was obtained from the University of British Columbia/Children's & Women's Health Centre of British Columbia Research Ethics Board. Written informed consent was obtained at each phase from mothers and verbal assent was obtained from children beginning at the age of 6 years. All SSRI-treated mothers had a diagnosed mood disorder; medication use was self-reported (Table 1). Inclusion criteria were singleton pregnancy, confirmed gestational age, ability to give informed consent, and no fetal anomalies detected by ultrasound. Exclusion criteria included bipolar disorder, illicit drug abuse, and significant medical, obstetrical, or fetal conditions. We had 254 mothers contact us to express interest in the study with 21 mothers excluded from the study and 42 mothers who chose to withdraw from the study (Fig. 1). The number of mother-child dyads at all data collection time points are summarized in Figure 1.

We assessed maternal depressive symptoms at second trimester enrolment in our study and again during the third trimester as part of the study design. This repeated assessment during pregnancy ensured we could confirm presence of a persistent prenatal depressed mood and not a short-term prenatal event. For the current study, differences in prenatal depression symptoms between mothers who participated and mothers who dropped out or where we were not able to obtain child behavior reports were examined. Mothers who participated at 12 years were less prenatally depressed (Hamilton Assessment of Depression [HAMD] third trimester, $M = 6.32$, $SD = 5.57$) than mothers who withdrew or had missing data ($M = 8.95$, $SD = 5.93$; $t = -3.14$, $p = 0.002$). However, there was no significant difference in the proportion of mothers who had been treated with an SSRI during pregnancy and participated at 12 years compared with mothers who had been treated with an SSRI during pregnancy and who withdrew or had missing data ($\chi^2(1) = 4.10$, $p > 0.05$). This cohort has been previously described in several studies.[9,12,19,24–26]

Procedures

Data collected included questionnaires assessing demographic information, maternal mood, objective performance-based measures, and subjective parental reports of the children's EFs at various points throughout the study (Fig. 1).

Depressive Symptoms

The HAMD,[27] a clinician-rated measure, was administered at various points throughout the longitudinal study (second trimester, third trimester, 6 weeks, 3 months, 6 months, 10 months, 6 years, and 12 years after the birth). For the HAMD, higher scores indicate higher levels of depression and only total scores were used. Self-reported depression symptoms were also collected using the Edinburgh Postnatal Depression Scale scores (EPDS) (second trimester and third trimester, plus 3 months, 6 months, and 10 months postpartum) and the Beck Depression Inventory scores (BDI) (3 years and 12 years after the birth). Predictor variables for the current study were limited to the HAMD at the third trimester, 6 years, and 12 years. The other measures of depressive symptoms, the self-reported EPDS and the BDI, were not used because of concerns about shared variance with the parent reports of EFs. Furthermore, these other measures of depressive symptoms (e.g., second trimester HAMD, EPDS, BDI) were used to estimate missing data as described in the statistical analyses section below.

Performance-based Measures of Executive Functions

Children completed two EF computer tasks at 6 and 12 years of age. The Flanker/Reverse Flanker task[28] consists of 3 blocks.

Table 1.

Descriptive Statistics for Mothers and Their Children

	Nonexposed (Total n = 115)	n	SSRI Exposed (Total n = 76)	n	T/χ^2 Value of the Difference Between the 2 Groups	*p*	Effect Size (*r*)[b]
Characteristics of the mothers							
Gestation in weeks at second trimester (SD)	26.65 (3.10)	108	24.98 (4.48)	73	2.98	0.003	0.22
Diagnosis at study entry (depression), n (%)	23 (20.2%)	114	62 (81.6%)	76	69.54[a]	<0.001	0.61[c]
Diagnosis at study entry (anxiety), n (%)	28 (24.6%)	114	54 (71.0%)	76	40.18[a]	<0.001	0.46[c]
Age at delivery (SD)	33.65 (5.04)	110	32.70 (5.43)	76	1.22	0.223	0.09
Education in years (SD)	17.73 (3.34)	113	16.36 (3.21)	76	2.83	0.005	0.20
Ethnicity					1.38[a]	0.495	0.09[c]
Caucasian, n (%)	47.3%	90	31.6%	60	0.00	> 0.999	0.00
Asian, n (%)	6.3%	12	2.6%	5	0.87	0.441	0.07
Other, n (%)	6.3%	12	5.8%	11	0.67	0.497	0.06
Prenatal SSRI treatment days, (SD)	0 (0.00)	115	235 (67.87)	75	−37.21	<0.001	0.94
Prenatal smoking, yes	105 (97.2%)	108	72 (97.3)	74		0.673[d]	
Prenatal alcohol use	3.42	109	4.05	75	−0.55	0.585	0.04
HAMD second trimester (SD)	6.68 (6.58)	109	11.90 (6.75)	73	−5.20	<0.001	0.36
HAMD third trimester (SD)	5.58 (5.58)	102	10.12 (5.87)	73	−5.26	<0.001	0.37
HAMD 6 yrs (SD)	6.28 (5.67)	72	10.98 (6.91)	51	−4.14	<0.001	0.35
HAMD 12 yrs (SD)	5.63 (5.70)	57	9.84 (6.41)	31	−3.17	<0.001	0.32
BDI 3 yrs (SD)	4.22 (4.39)	88	8.12 (5.88)	59	−4.59	<0.001	0.36
BDI 12 yr (SD)	6.79 (6.33)	14	7.50 (5.54)	6	−0.24	0.814	0.06
Characteristics of the children							
Gestational age at birth	39.75 (1.75)	110	39.05 (1.60)	75	2.80	0.006	0.20
Sex at birth (females), n (%)	58 (52.7%)	110	42 (55.2%)	75	0.19[a]	0.764	0.03[c]
Delivery mode (caesarean section), n (%)	30 (23.7%)	110	22 (29.3)	75	0.09[a]	0.760	0.02[c]
Birth weight (g) (SD)	3492.05 (545.32)	110	3323.12 (517.61)	75	2.11	0.036	0.15
Birth length (cm) (SD)	51.65 (2.82)	109	50.61 (2.36)	75	2.63	0.009	0.19
Apgar score (1 min) (SD)	8.24 (1.39)	110	7.48 (1.63)	75	3.38	0.001	0.24
Apgar score (5 min) (SD)	8.99 (0.57)	110	8.80 (0.74)	73	1.99	0.048	0.15
Mean age at 3 yrs (SD)	3.53 (0.57)	88	3.85 (0.63)	59	−3.22	0.002	0.26
Mean age at 6 yrs (SD)	5.81 (0.59)	89	6.12 (0.79)	56	−2.73	0.007	0.22
Mean age 12 yrs (SD)	11.68 (1.11)	78	11.88 (1.17)	40	−0.65	0.518	0.06
Flanker/RF mixed block % correct at 6 yrs (SD)	66.7 (19)	73	68.0 (15)	47	−0.35	0.730	0.03
Flanker/RF mixed block RT at 6 yrs in ms (SD)	1743.63 (452.94)	73	1746.16 (457.78)	47	−0.03	0.976	<0.01
Flanker/RF mixed block % correct at 12 yrs (SD)	81.2 (11.0)	62	81.6 (12.9)	34	−0.15	0.884	0.02
Flanker/RF mixed block RT at 12 yrs in ms (SD)	857.13 (116.04)	62	887.10 (121.08)	34	−1.19	0.236	0.12
HF mixed block % correct at 6 yrs (SD)	66.2 (0.23)	74	67.7 (0.24)	48	−0.34	0.731	0.03
HF mixed block RT at 6 yr in ms (SD)	1172.00 (155.85)	73	1176.32 (132.89)	48	−0.16	0.875	0.01
HF mixed block % correct at 12 yrs (SD)	71.56 (0.18)	61	72.32 (0.21)	35	−0.18	0.855	0.02
HF mixed block RT at 12 yrs in ms (SD)	600.74 (49.38)	61	610.16 (44.20)	35	−0.93	0.353	0.10
BRIEF GEC T score at 6 yrs	53.27 (8.81)	88	53.41 (10.23)	51	−0.08	0.993	0.01
Above clinical threshold, n (%)	9 (10.2%)	88	8 (15.7%)	51	0.90[a]	0.249	0.08[c]
BRIEF GEC T score at 12 yrs	53.34 (12.96)	73	59.30 (12.20)	37	−2.32	0.022	0.22
Above clinical threshold, n (%)	14 (19.2%)	73	13 (35.1%)	37	3.38[a]	0.099	0.18[c]

Mean values are provided unless indicated otherwise. SSRI = Selective Serotonin Reuptake Inhibitor; Asian = those who self-identified as oriental; other = those who chose to self-identify as the following: Indian (n = 6), Latin (n = 5), Oriental/White (n = 3), Native North American Indian (n = 2), and 1 mother in each of the following self-identifying categories: Filipino/Polynesian, Black, Greek, Israeli, Eurasian, Jewish, West Indian, and preferred not to respond; SSRI treatment days = number of days of prenatal SSRI treatment (range = 41–294 days), no information collected on timing of treatment but most mothers were taking SSRIs at the time of conception; prenatal smoking = yes = <20 cigarettes per day; prenatal alcohol use = maternal alcohol consumption in single drinks during entire pregnancy; HAMD = Hamilton Rating Scale for Depression; BDI = Beck Depression Inventory; RF = Reverse Flanker; % = percentage correct; RT = reaction time; ms = milliseconds; HF = Hearts and Flowers task block 3; BRIEF GEC T score = Behavior Rating Inventory of Executive Function Global Executive Composite, with higher T scores indicating higher levels of executive dysfunction; clinical threshold = number of participants with a T score of 65 or higher.

[a] Chi-square value.

[b] Cohen (1988, 1992) suggests low effect = 0.10, medium effect = 0.30, large effect = 0.50.

[c] Phi value.

Block 1 presents the classic Flanker paradigm.[29] Children are to press the key on the side of the keyboard that represents the direction in which the middle stimulus is pointing. All the stimuli are blue in block 1. Block 2 presents the Reverse Flanker condition, where participants focus on the Flankers (the outside stimuli) and ignore the center stimulus. All Flanking stimuli always point in the same direction. In contrast to the previous block, children are instructed to press the key that represents the direction in which the outside stimuli are pointing. All the stimuli are pink in block 2. Block 3 is the mixed block, where

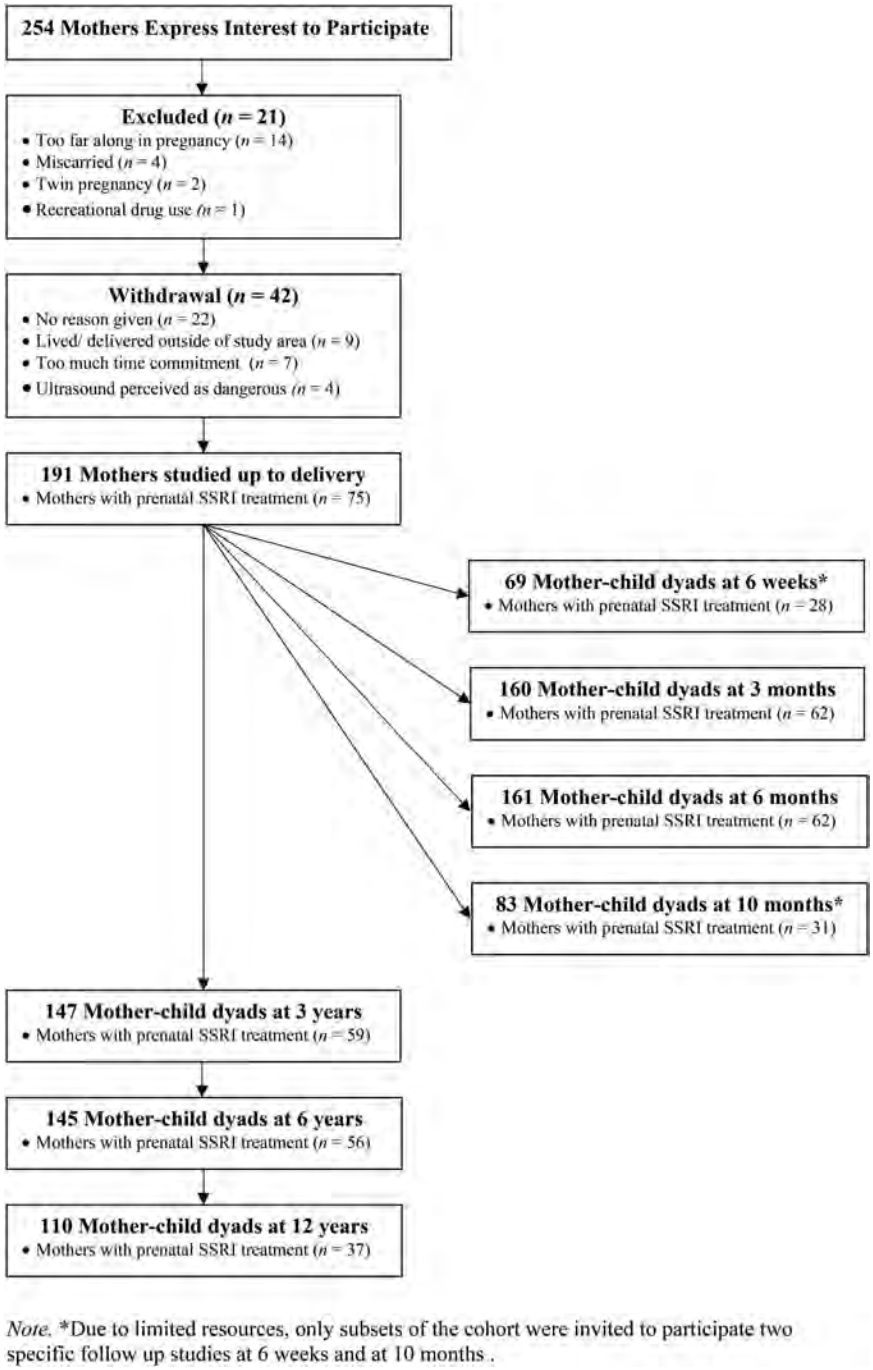

Figure 1. Study flow chart representing recruitment, dropout, and follow-up of study participants. *Because of limited resources, only subsets of the cohort were invited to participate 2 specific follow-up studies at 6 weeks and at 10 months.

standard Flanker trials in blue and reverse Flanker trials in pink are randomly intermixed, requiring flexible application of the rules for each. After determining which rule is relevant, a participant determines which way the target is pointing and uses that information to determine which key to press. Accuracy scores (percentage of correct responses, calculated by dividing the number of correct responses by the total number of responses) and reaction time (in milliseconds) from block 3 were used in the analyses as block 3 placed the greatest demands on EFs. This task has been used in a number of studies with children.[30,31]

Children also completed the Hearts and Flowers (HF) task, a computerized measure which has been validated with children 4 to 13 years of age.[32] This task consists of 3 blocks. Block 1 (the Congruent Block) presents a picture of a heart and children are to press the key on the same side of the keyboard as the heart appears on. Block 2 (the Incongruent Block) presents a picture of a flower and children are to press the key on the side opposite to where the flower appears. Block 3 (the Mixed Block) presents congruent and incongruent trials randomly interspersed. Percent correct and reaction time from block 3 were used in the analyses as block 3 placed the greatest demands on EFs.

Reports of Executive Functions

Mothers completed the BRIEF parent form, a well-known standardized measure of EFs in children between the ages of 5 to 18 years,[33] when their children were 6 and 12 years old. The Global Executive Composite (GEC) score was used, which is the overall score across all responses on the measure. Results for the current study are reported as T scores, with higher scores indicating greater perceived impairment (i.e., worse EFs).

Statistical Analyses

In this longitudinal cohort, not all mothers and their children participated at each time point and missing data (HAMD third trimester n = 4, 6 years n = 22, 12 years n = 23) were imputed using Maximum Likelihood estimation with SYSTAT, which uses the expectation maximization algorithm to estimate missing data from key variables.[34] For this study, variables used to estimate missing data were as follows: clinician-rated depression using HAMD scores (second trimester and third trimester, plus 6 weeks, 3 months, 6 months, 10 months, 6 years, and 12 years after the birth), EPDS (second trimester and third trimester, plus 3 months, 6 months, and 10 months postpartum), and BDI (3 and 12 years after the birth), based on the recommendation from Little et al.[35] to use all the available variables in the dataset to improve accuracy.

Differences in mothers' and children's characteristics were compared between mothers (with and without prenatal SSRI treatment) and children (with and without SSRI exposure) using independent-samples t tests or χ^2 tests as appropriate. To screen for outliers, all variables were converted to z-scores and no outliers were observed using a critical cutoff value of ± 3.29. We conducted correlational analyses to summarize the relationships between variables and to determine the strength of these relationships, whether they were negative, positive, or zero and to allow other researchers to replicate the analysis, providing reproducibility and transparency.

General estimating equation (GEE) modeling[36] were used to examine associations between depressive symptoms, SSRI exposure, and EFs. GEE models were used to examine child's age (6 and 12 years) and group (mother with and without prenatal SSRI treatment), with prenatal maternal depressive symptoms (HAMD third trimester) and later maternal depressive symptoms (HAMD at 6 years) as covariates, in relation to the 5 EF outcome variables. For all GEE models, interactions were also tested (SSRI exposure and third trimester depressive symptoms) in addition to later maternal depressive symptoms (HAMD at 12 years). As interactions and the later maternal depressive symptoms did not contribute significantly to the results, they were dropped from the final models presented.

We chose to use the HAMD at the third trimester instead of the HAMD at the second trimester because this was the closest measurement during pregnancy relative to the other time points (at 6 and 12 years). However, the second and third trimesters are quite different regarding fetal development and maternal stressors/experiences. To address this possibility, we re-ran all the models again that used only HAMD at the second trimester and the outcomes were similar. We also re-ran the models again that used a computed average of the two HAMD scores and the outcomes were similar. Thus, as outcomes were similar for all 3 measures, we used HAMD at the third trimester for all models presented.

All analyses were conducted using SPSS version 19 and SYSTAT 12. As our cohort was a convenience sample that included 5 pairs of siblings, which introduced a risk of shared variance, we re-ran all analyses again by randomly excluding 1 of the siblings from each pair. There were no significant differences in outcomes. Thus, these 5 children were retained in the final sample.

RESULTS

Descriptive Statistics

Mothers with prenatal SSRI treatment had more depressive symptoms during the third trimester and when their child was 6 and 12 years old compared with mothers without prenatal SSRI treatment (Table 1). All group HAMD mean values were <12, which is below the typical clinical cutoff for a diagnosis of moderate depression (17–23).[37] As we were interested in the full range of depressive symptoms, we did not limit our study to only mothers who were above the clinical cutoff for depression at each time of assessment. Although mothers with prenatal SSRI treatment also had significantly fewer years of education (16.36) than mothers not treated with an SSRI (17.73), both groups were relatively highly educated. Mothers with prenatal SSRI treatment reported significantly poorer EFs at 12 years (59.30, higher scores indicating higher executive dysfunction) than mothers not treated with an SSRI (53.34). However, we failed to observe any other significant group differences in all remaining EF measures (Table 1).

Relations Between Depressive Symptoms, Education, and Executive Functions

Tables 2 and 3 present correlational analyses for measures of maternal education, depressive symptoms, and EFs for the entire sample. At 6 years, children were more accurate on the HF task if their mothers reported fewer depressive symptoms during the third trimester and at 6 months postpartum (Table 2). Furthermore, at 6 years, children took longer on the Flanker/Reverse Flanker task if their mother had fewer depressive symptoms at 6 years. At 12 years, children took longer on the HF task if their mother had more depressive symptoms when the child was 6 and 12 years old. Table 3 shows that mothers with fewer depressive symptoms at all periods (second trimester to 12 years) were more likely to report less evidence of executive dysfunction (i.e., better EFs) in their children at 6 and 12 years of age. Furthermore, mothers with more education were more likely to have children who they reported had lower levels of executive dysfunction (i.e., better EFs) at 6 and 12 years of age.

In terms of associations between standardized scores (T scores) on the BRIEF GEC and performance-based EF tasks, there were significant correlations between the Flanker/Reverse Flanker task at 6 years (percentage of correct responses) and the BRIEF global score at 6 years ($r = -0.31$, $p = 0.001$) and the BRIEF global score at 12 years ($r = -0.30$, $p = 0.005$) (data not shown in Tables; the negative correlation is because of higher BRIEF scores indicating worse EFs). In other words, mothers who had children with better scores on Flanker/Reverse Flanker at 6 years were also more likely to report less executive dysfunction in their children at 6 and again at 12 years. All other associations were not significant.

Most associations between the two EF tasks (Flanker/Reverse Flanker, HF) were significant (rs ranging from -0.44 to 0.66, data not shown in tables). The only exception was for Flanker/Reverse Flanker percentage correct at 6 years; this outcome was

Table 2.

Descriptive Correlational Analyses Between Measures of Maternal Education, Maternal Depressive Symptoms, and Performance-Based EFs in Children

Variable	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Birthing parent education	−0.22**	−0.24**	−0.23**	−0.25**	−0.20**	−0.04	0.02	−0.07	0.11	0.05	−0.05	0.00	−0.04
2. HAMD second trimester	—	0.71**	0.58**	0.64**	0.48**	−0.14	−0.05	−0.13	0.03	−0.09	0.13	−0.08	0.17
3. HAMD third trimester		—	0.67**	0.59**	0.50**	−0.10	0.14	−0.24**	0.16	−0.11	0.14	−0.12	0.18
4. HAMD 6 mo postpartum			—	0.57**	0.63**	−0.07	0.17	−0.26**	0.13	−0.09	0.15	−0.10	0.08
5. HAMD 6 yrs				—	0.57**	−0.07	−0.21*	−0.00	−0.13	0.08	−0.04	−0.01	0.21*
6. HAMD 12 yrs					—	−0.19*	0.03	−0.16	−0.03	−0.19	0.18	−0.14	0.25*
7. Flanker/Reverse Flanker % correct at 6 yrs						—	0.20*	0.02	0.04	0.03	−0.04	0.01	0.04
8. Flanker/Reverse Flanker RT at 6 yrs							—	−0.60**	0.64**	−0.38**	0.24**	−0.42**	0.27*
9. HF % correct at 6 yrs								—	−0.52**	0.47**	−0.29**	0.66**	−0.14
10. HF RT on correct trials at 6 yrs									—	−0.25*	0.28**	−0.45**	0.26*
11. Flanker/Reverse Flanker % correct at 12 yrs										—	−0.44**	0.55**	−0.28**
12. Flanker/Reverse Flanker RT at 12 yrs											—	−0.44**	0.53**
13. HF % correct at 12 yrs												—	−0.42**
14. HF RT on correct trials at 12 yrs													—

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
EFs, executive functions; HAMD, Hamilton Rating Scale for Depression; HF, Hearts and Flowers task block 3; Flanker, Flanker/Reverse Flanker task block 3; RT, reaction time.

only significantly associated with Flanker/Reverse Flanker reaction time at 6 years and nothing else.

Performance-Based Measure of Executive Functions

Flanker/Reverse Flanker Task. The first GEE model showed that older children and children who had a mother with fewer prenatal depression symptoms at third trimester showed greater accuracy on Flanker/Reverse Flanker (Table 4). There was no evidence of a significant association with SSRI exposure and maternal depressive symptoms at 6 years on this measure of EFs. In reaction time, the second GEE model showed that older children and children who had a mother with fewer prenatal depression symptoms (at third trimester and at 6 years) were faster on the Flanker/Reverse Flanker (Table 4). There was no evidence of a significant association between reaction time on this task and SSRI exposure (Table 4).

Hearts and Flowers Task. The third GEE model showed that older children and children whose mother had fewer prenatal depression symptoms at third trimester responded more accurately on the HF task (Table 4). There was no evidence of a significant association with SSRI exposure and maternal depressive symptoms at 6 years on this measure of EFs. In reaction time, the fourth GEE model showed that older children and children who had a mother with fewer prenatal depression symptoms (at third trimester and at 6 years) were faster on the HF task (Table 4). There was no evidence of significant associations between reaction time on this task and SSRI exposure.

Parental Report of Executive Functions on the Behavior Rating Inventory of Executive Function

The fifth GEE model showed that children whose mothers had fewer prenatal depression symptoms at third trimester were reported by their mothers to show better EF performance (less EF dysfunction; Table 4). There was no evidence of significant

Table 3.

Descriptive Correlational Analyses Between Measures of Maternal Parent Education, Maternal Depressive Symptoms, and Maternal Ratings of EFs in Children

Variable	2	3	4	5	6	7	8
1. Maternal education	−0.22**	−0.24**	−0.23**	−0.25**	−0.20**	−0.23**	−0.32**
2. HAMD second trimester	—	0.71**	0.58**	0.64**	0.48**	0.26**	0.35**
3. HAMD third trimester		—	0.67**	0.59**	0.50**	0.28**	0.24**
4. HAMD 6 mo postpartum			—	0.57**	0.63**	0.25**	0.26**
5. HAMD 6 yrs				—	0.57**	0.20**	0.28**
6. HAMD 12 yrs					—	0.18**	0.31**
7. BRIEF GEC T score at 6 yrs						—	0.51**
8. BRIEF GEC T score at 12 yrs							—

BRIEF GEC, Behavior Rating Inventory of Executive Function Global Executive Composite; EFs, executive function; HAMD, Hamilton Rating Scale for Depression.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

Table 4.

Generalized Estimating Equation Regressions (Main Analyses)

Task and Variable	B	Standard Error	95% Confidence Interval		p
Flanker block 3% correct					
Age	−0.14	0.02	−0.18	−0.10	**< 0.001**
HAMD third trimester	−0.01	0.00	−0.01	0.00	0.032
HAMD at 6 yrs	0.00	0.00	−0.00	0.01	0.696
SSRI exposure	−0.03	0.03	−0.08	0.02	0.258
Flanker block 3 RT					
Age	863.41	40.13	784.75	942.07	**< 0.001**
HAMD third trimester	17.28	5.75	6.00	28.55	0.003
HAMD at 6 yrs	−19.12	3.93	−23.83	−8.42	**< 0.001**
SSRI exposure	2.74	60.82	−116.46	121.94	0.964
HF block 3% correct					
Age	−0.05	0.02	−0.09	−0.01	0.023
HAMD third trimester	−0.01	0.00	−0.02	−0.01	0.001
HAMD at 6 yrs	0.00	0.00	−0.00	0.01	0.172
SSRI exposure	−0.06	0.04	−0.14	0.01	0.107
HF block 3 RT					
Age	566.48	13.45	540.13	592.83	**< 0.001**
HAMD third trimester	5.09	1.98	1.22	8.97	0.010
HAMD at 6 yrs	−2.92	1.42	−5.71	−0.13	0.040
SSRI exposure	7.29	22.02	−35.87	50.46	0.741
BRIEF GEC score					
Age	−2.13	1.11	−4.31	0.05	0.055
HAMD third trimester	0.38	0.16	0.07	0.69	0.017
HAMD at 6 yrs	0.26	0.17	−0.07	0.59	0.124
SSRI exposure	0.52	1.74	−2.90	3.93	0.767

BRIEF GEC, Behavior Rating Inventory of Executive Function Global Executive Composite; B, nonstandardized regression coefficient; Flanker, Flanker/Reverse Flanker; HF, Hearts and Flowers task; HAMD, Hamilton Rating Scale for Depression; prenatal mood, HAMD at third trimester; RT, reaction time; SSRI, selective serotonin reuptake inhibitor.
Bold value indicates $p < 0.001$.

associations between ratings on the BRIEF, age, SSRI exposure, and depression symptoms at 6 years.

DISCUSSION

We examined longitudinal associations between children's EFs at ages 6 and 12 years, mother's prenatal depressive symptoms, mother's later depressive symptoms at 6 years, and mother's prenatal SSRI antidepressant treatment. At the outset, we sought to identify a long-term effect of prenatal exposure to SSRIs. However, what emerged was that prenatal depressive symptoms, not prenatal SSRI exposure alone, seems to have a long-lasting impact on EFs in children that continues into preadolescence. As expected, our longitudinal results showed that all children were more accurate and faster as they got older on the most demanding portions of the Flanker/Reverse Flanker and HF tasks (the Mixed Blocks, which tax all 3 core EFs: working memory, inhibitory control, and cognitive flexibility), consistent with previous research.[20,21,28,30–32,38] We found that prenatal SSRI exposure alone was not associated with performance on the two EF tasks. These results are consistent with another study with 5- and 6-year-olds, which found no significant differences in performance on an EF task (modified Attentional Network task) between children with prenatal SSRI exposure, medically untreated perinatal depression exposure, and no exposure.[15]

Correlational results showed that children who were more accurate on HF at 6 years of age were likely to have mothers with fewer depressive symptoms during the third trimester and at 6 months postpartum. These results suggest the long-term impact of perinatal mental health on later child development of EFs, consistent with previous research.[39–42] Interestingly, the only significant correlation with Flanker/Reverse Flanker showed that children at 6 years who were slower on this task were likely to have a mother with fewer depressive symptoms at 6 years ($r = -0.21$). This result was unexpected. However, it is worth noting that a nonsignificant negative association was also observed in reaction time for HF at 6 years and maternal depressive symptoms at 6 years ($r = -0.13$), increasing our confidence in these results. One possible explanation is that children exposed to a mother with fewer depressive symptoms may be more focused on doing the task well rather than rushing through the task quickly. This possibility is supported by evidence that children whose accuracy was better on HF at 6 years were likely to have mothers with fewer depressive symptoms at 6 years, as mentioned above. It is also worth noting that this finding was only observed when children were 6 years of age and not 12 years of age, suggesting that age may be a contributing factor to these results.

Maternal Reports of Executive Functions

As expected, longitudinal analysis showed that older children and children who had mothers with fewer clinician-measured prenatal depression symptoms were likely to be seen by their mothers as having better EFs. We failed to find evidence that prenatal SSRI exposure alone was associated with EFs at 12 years, which is consistent with our findings with this same cohort at 6 years[19] and previous research that used parent rating of children's EFs at 4 years (BRIEF GEC).[17,18] Yet, it is still possible that subtle cognitive problems might emerge at a later age and continued assessment into young adulthood is needed before firmer conclusions can be made.

Associations Between Executive Function Measures

The 2 EF tasks (Flanker/Reverse Flanker, HF) were significantly associated with each other, suggesting that they are both tapping similar EFs. Based on previous findings, we had expected there would be no significant correlations between performance-based measures of EFs and parental ratings of EFs.[22] However, mothers whose children were more accurate on Flanker/Reverse Flanker at 6 years also were more likely to report less executive dysfunction in their children at 6 and 12 years. No other associations were significant. Given that most associations between EF performance and parent-report measures were not significant (n = 16), these findings emphasize the inherent differences in the assessment of EF skills using objective performance-based measures versus subjective informant rating scales that focus on EF deficits.[22,38]

Clinical Implications

Results from the current study are especially relevant for interventions during and after pregnancy. Specifically, we found that both prenatal and postnatal measures of depressive symptoms were related to EFs in children. These findings highlight the importance of ongoing assessments of maternal mental health long after delivery and assessment of mother's mental health beginning long before a child's EFs are assessed. Additional research is critical to determine risks related to maternal depressive symptoms and identify who may benefit from prenatal and postnatal antidepressant treatment.

Limitations

A few key limitations should be acknowledged. Mothers in our cohort were relatively highly educated. Thus, effects reported here might not generalize across the full socioeconomic spectrum. Second, although our study measures of maternal depressive symptoms were comprehensive (clinician rates and self-report), we did not measure children's attachment and affect, both of which have been suggested to mediate the impact of maternal depressive symptoms on children's EFs. For example, a loving, secure connection (attachment relationship) between the mother and child can buffer against the negative effects of all manner of early-life stressors including a mother's tendencies toward depression.[43] Third, genetics and the everyday environment could also have contributed to the impact of exposure to mothers' depressive symptoms and SSRI antidepressant treatment. Fourth, given that SSRI treated mothers remained significantly more depressed long after pregnancy, our findings may also reflect a failure to remit symptoms. Thus, these factors need to be considered by future researchers. Finally, because of our sample size, we had to limit the number of covariates used in the study. However, it is possible for larger population-based studies to address this limitation in the future.

CONCLUSIONS

To our knowledge, this is the only study that has used clinician-rated measures of maternal depressive symptoms (Hamilton Rating Scale for Depression), performance-based measures of EFs, and informant reports of EFs to better understand the possible impact of prenatal SSRI exposure on children's cognitive development over 12 years. Prenatal exposure to SSRIs were not associated with performance-based measures of EFs, nor informant reports of EFs, once maternal depressive symptoms were controlled for. Additional research with a larger sample beyond early adolescence is needed to examine the impact of prenatal maternal mental health and prenatal SSRI exposure on long-term patterns of cognitive development in children.

ACKNOWLEDGMENTS

The authors are grateful to the mothers and their children who participated and contributed to this research program. The authors also thank Ms. Colleen Pawliuk, our librarian, for her assistance.

REFERENCES

1. Diamond A. Executive functions. Annu Rev Psychol. 2013;64:135–168.
2. Miyake A, Friedman NP, Emerson MJ, et al. The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. Cogn Psychol. 2000;41:49–100.
3. Hendry A, Jones EJ, Charman T. Executive function in the first three years of life: precursors, predictors and patterns. Develop Rev. 2016;42:1–33.
4. Moffitt TE, Arseneault L, Belsky D, et al. A gradient of childhood self-control predicts health, wealth, and public safety. Proc Natl Acad Sci USA. 2011;108:2693–2698.
5. Power J, van Ijzendoorn M, Lewis AJ, et al. Maternal perinatal depression and child executive function: a systematic review and meta-analysis. J Affect Disord. 2021;291:218–234.
6. Woolhouse H, Gartland D, Mensah F, et al. Maternal depression from early pregnancy to 4 years postpartum in a prospective pregnancy cohort study: implications for primary health care. BJOG. 2015;122:312–321.
7. O'Donnell KJ, Meaney MJ. Fetal origins of mental health: the developmental origins of health and disease hypothesis. Am J Psychiatry. 2017;174:319–328.
8. Fay-Stammbach T, Hawes DJ, Meredith P. Parenting influences on executive function in early childhood: a review. Child Dev Perspect. 2014;8:258–264.
9. Weikum WM, Brain U, Chau CM, et al. Prenatal serotonin reuptake inhibitor (SRI) antidepressant exposure and serotonin transporter promoter genotype (SLC6A4) influence executive functions at 6 years of age. Front Cell Neurosci. 2013;7:180.
10. Charlton R, Jordan S, Pierini A, et al. Selective serotonin reuptake inhibitor prescribing before, during and after pregnancy: a population-based study in six European regions. BJOG. 2015;122:1010–1020.
11. Homberg JR, Lesch K-P. Looking on the bright side of serotonin transporter gene variation. Biol Psychiatry. 2011;69:513–519.
12. Erickson NL, Hancock GR, Oberlander TF, et al. Prenatal SSRI antidepressant use and maternal internalizing symptoms during pregnancy and postpartum: exploring effects on infant temperament trajectories for boys and girls. J Affect Disord. 2019;258:179–194.
13. Malm H, Brown AS, Gissler M, et al. Gestational exposure to selective serotonin reuptake inhibitors and offspring psychiatric disorders: a national register-based study. J Am Acad Child Adolesc Psychiatry. 2016;55:359–366.
14. Rotem-Kohavi N, Oberlander TF. Variations in neurodevelopmental outcomes in children with prenatal SSRI antidepressant exposure. Birth Defects Res. 2017;109:909–923.
15. Hermansen TK, Yrttiaho S, Røysamb E, et al. Perceptual interference processing in preschool children, with and without prenatal exposure to selective serotonin reuptake inhibitors. Psychopharmacology (Berl). 2017;234:339–351.
16. Isquith PK, Roth RM, Gioia G. Contribution of rating scales to the assessment of executive functions. Appl Neuropsychol Child. 2013;2:125–132.
17. El Marroun H, White TJ, Fernandez G, et al. Prenatal exposure to selective serotonin reuptake inhibitors and non-verbal cognitive functioning in childhood. J Psychopharmacol. 2017;31:346–355.
18. Galbally M, Lewis AJ, Buist A. Child developmental outcomes in preschool children following antidepressant exposure in pregnancy. Aust N Z J Psychiatry. 2015;49:642–650.
19. Hutchison SM, Mâsse LC, Brain U, et al. A 6-year longitudinal study: are maternal depressive symptoms and selective serotonin reuptake inhibitor (SSRI) antidepressant treatment during pregnancy associated with everyday measures of executive function in young children? Early Hum Develop. 2019;128:21–26.
20. Reuter E-M, Vieluf S, Koutsandreou F, et al. A non-linear relationship between selective attention and associated ERP markers across the lifespan. Front Psychol. 2019;10:30.
21. McDermott JM, Pérez-Edgar K, Fox NA. Variations of the flanker paradigm: assessing selective attention in young children. Behav Res Methods. 2007;39:62–70.
22. Toplak ME, West RF, Stanovich KE. Practitioner review: do performance-based measures and ratings of executive function assess the same construct? J Child Psychol Psychiatry. 2013;54:131–143.
23. McAuley T, Chen S, Goos L, et al. Is the behavior rating inventory of executive function more strongly associated with measures of impairment or executive function? J Int Neuropsychol Soc. 2010;16:495–505.
24. Hutchison SM, Brain U, Grunau RE, et al. Associations between maternal depressive symptoms and selective serotonin reuptake inhibitor antidepressant treatment on internalising and anxiety behaviours in children: 12-year longitudinal study. BJPsych Open. 2023;9:e26.
25. Hutchison SM, Mâsse LC, Glier MB, et al. Impact of prenatal selective serotonin reuptake inhibitor antidepressant exposure and maternal mood on physical activity, dietary intake, and markers of adiposity at age 6 years. J Dev Behav Pediatr. 2019;40:266–274.
26. Zusman EZ, Chau CM, Bone JN, et al. Prenatal serotonin reuptake inhibitor antidepressant exposure, SLC6A4 genetic variations, and cortisol activity in 6-year-old children of depressed mothers: a cohort study. Dev Psychobiol. 2023;65:e22425.
27. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56–62.
28. Schonert-Reichl KA, Oberle E, Lawlor MS, et al. Enhancing cognitive and social–emotional development through a simple-to-administer mindfulness-based school program for elementary school children: a randomized controlled trial. Dev Psychol. 2015;51:52–66.
29. Eriksen BA, Eriksen CW. Effects of noise letters upon the identification of a target letter in a nonsearch task. Percept Psychophys. 1974;16:143–149.
30. Zaitchik D, Iqbal Y, Carey S. The effect of executive function on biological reasoning in young children: an individual differences study. Child Dev. 2014;85:160–175.

31. Liu J, Li Y, Zhou T, et al. Relationship between gross motor skills and inhibitory control in preschool children: a pilot study. Front Hum Neurosci. 2022;16:848230.
32. Diamond A, Barnett WS, Thomas J, et al. Preschool program improves cognitive control. Science. 2007;318:1387–1388.
33. Gioia GA, Isquith PK, Guy S, et al. BRIEF: Behavior Rating Inventory of Executive Function; 2000.
34. Enders CK. A primer on the use of modern missing-data methods in psychosomatic medicine research. Psychosom Med. 2006;68:427–436.
35. Little TD, Card NA, Preacher KJ, et al. Modeling Longitudinal Data From Research on Adolescence; 2009.
36. Zeger SL, Liang K-Y. Longitudinal data analysis for discrete and continuous outcomes. Biometrics. 1986;42:121–130.
37. Zimmerman M, Martinez JH, Young D, et al. Severity classification on the Hamilton depression rating scale. J Affect Disord. 2013;150:384–388.
38. Wright A, Diamond A. An effect of inhibitory load in children while keeping working memory load constant. Front Psychol. 2014;5:213.
39. Gueron-Sela N, Camerota M, Willoughby MT, et al. Maternal depressive symptoms, mother-child interactions, and children's executive function. Dev Psychol. 2018;54:71–82.
40. Bechtiger L, Steinhoff A, Dollar JM, et al. Pathways from maternal depressive symptoms to children's academic performance in adolescence: a 13-year prospective-longitudinal study. Child Dev. 2022;93:388–404.
41. Hughes C, Ensor R. Independence and interplay between maternal and child risk factors for preschool problem behaviors? Int J Behav Dev. 2009; 33:312–322.
42. Pearson RM, Bornstein MH, Cordero M, et al. Maternal perinatal mental health and offspring academic achievement at age 16: the mediating role of childhood executive function. J Child Psychol Psychiatry. 2016;57: 491–501.
43. Bernier A, Carlson SM, Deschênes M, et al. Social factors in the development of early executive functioning: a closer look at the caregiving environment. Dev Sci. 2012;15:12–24.