In Utero Antidepressants and Neurodevelopmental Outcomes in Kindergarteners

Deepa Singal, PhD,[c] Dan Chateau, PhD,[c] Shannon Struck, BHEcol,[c] Janelle Boram Lee, BA,[c] Matthew Dahl, MSc,[c] Shelly Derksen, MSc,[c] Laurence Y. Katz, MD,[d] Chelsea Ruth, MD,[a] Ana Hanlon-Dearman, MD,[b] Marni Brownell, PhD[c]

abstract

OBJECTIVES: To determine if in utero selective serotonin reuptake inhibitor (SSRI) or selective serotonin norepinephrine inhibitor (SNRI) exposure is associated with developmental vulnerability in kindergarten among children whose mothers were diagnosed with prenatal mood or anxiety disorder.

METHODS: Linkable administrative data were used to create a population-based cohort of 266 479 mother-child dyads of children born in Manitoba, Canada, between 1996 and 2014, with follow-up through 2015. The sample was restricted to mothers who had a mood or anxiety disorder diagnosis between 90 days before conception (N = 13 818). Exposed women had ≥2 SSRI or SNRI dispensations during pregnancy (n = 2055); unexposed mothers did not have a dispensation of an SSRI or SNRI during pregnancy (n = 10 017). The Early Development Instrument (EDI) was used to assess developmental health in kindergarten children. The EDI is a 104-component kindergarten teacher-administered questionnaire, encompassing 5 developmental domains.

RESULTS: Of the 3048 children included in the study who met inclusion criteria and had an EDI, 21.43% of children in the exposed group were assessed as vulnerable on 2 or more domains versus 16.16% of children in the unexposed group (adjusted odds ratio = 1.43; 95% confidence interval 1.08–1.90). Children in the exposed group also had a significant risk of being vulnerable in language and/or cognition (adjusted odds ratio = 1.40; 95% confidence interval 1.03–1.90).

CONCLUSIONS: Exposure to SSRIs or SNRIs during pregnancy was associated with an increased risk of developmental vulnerability and an increased risk of deficits in language and/or cognition. Replication of results is necessary before clinical implications can be reached.

[a]*Section of Neonatology, Department of Pediatrics and Child Health,* [b]*Section of Developmental Pediatrics, Department of Pediatrics and Child Health Policy, and* [c]*Department of Community Health Sciences, Manitoba Centre for Health Policy, and* [d]*Department of Psychiatry, Child and Adolescent Psychiatry Health Sciences Centre, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada*

Dr Singal conceptualized the study, acquired the data, and wrote the primary manuscript draft; Dr Brownell conceptualized the study, critically reviewed drafts of the manuscript, and provided supervision; Dr Chateau conceptualized the analysis plan, critically reviewed drafts of the manuscript, and provided supervision; Mr Dahl and Ms Derksen ran all statistical analysis and revised drafts of the manuscript; Ms Struck and Ms Lee provided research support and helped draft the manuscript; Drs Katz, Ruth, and Hanlon-Dearman contributed to the conceptualization of the study, critically reviewed drafts of the manuscript, and provided content expertise; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2019-1157

WHAT'S KNOWN ON THIS SUBJECT: Children exposed in utero to antidepressants have higher rates of adverse outcomes in infancy. However, there are limited studies that investigate the long-term neurodevelopmental effects of in utero exposure to these medications on early childhood development.

WHAT THIS STUDY ADDS: Children of mothers diagnosed with a mood or anxiety disorder who took serotonergic antidepressants during pregnancy had an increased risk of developmental vulnerability and deficits in language and cognition in kindergarten.

To cite: Singal D, Chateau D, Struck S, et al. In Utero Antidepressants and Neurodevelopmental Outcomes in Kindergarteners. *Pediatrics.* 2020;145(5):e20191157

Up to 12% of women are diagnosed with perinatal depression.[1] Selective serotonin reuptake inhibitors (SSRIs) are one of the most commonly prescribed antidepressant medications, including in pregnancy[2]; 10% of women are prescribed SSRIs during pregnancy.[3,4] In numerous studies, authors have investigated adverse infant outcomes associated with in utero antidepressant exposure, including neonatal adaptation syndrome,[5–7] pulmonary hypertension,[8–10] cardiac malformations,[5,11] low birth weight,[12–14] small for gestational age,[12,13] and motor and cognitive outcomes.[15–18] These studies yielded conflicting results and revealed small absolute risks when comparing children exposed in utero to untreated maternal depression.[8,19]

Fewer studies have been used to investigate long-term neurodevelopmental effects of in utero exposure to antidepressants. Recent studies yielded conflicting results regarding increased risk of autism spectrum disorder[20–23] and attention-deficit/hyperactivity disorder[24–26] in children exposed to in utero antidepressants. Several studies indicated[5,13,27] difficulties in psychomotor function and motor quality among infants exposed to antidepressant medications in utero. A recent population-based analysis from Finland[28] revealed an increased risk of speech and/or language disorders in children of mothers diagnosed with psychiatric disorders who used SSRIs during pregnancy. These investigations indicate in utero SSRI exposure may have implications on fetal brain development and sustained cognitive impairment into childhood.

Educational outcomes are important indicators of child neurodevelopment; however, data investigating these additional indicators of development are scarce. Two studies have been used to examine the association between in utero antidepressant exposure and elementary school outcomes in offspring.[29,30] Authors of a population-based study in Denmark[29] found an association between in utero exposure to SSRIs and delayed elementary school entry in children. A study in a US hospital setting was used to examine preschool outcomes of language skills and cognitive functions, and the authors found a significant relationship with prenatal SSRI exposure.[30] Findings should be replicated in other settings, using validated measures of educational achievement to reach conclusions about the effect of in utero serotonergic antidepressant exposure and early childhood development.

In this study, we use a North American population-based cohort to investigate the impact of in utero SSRI and serotonin norepinephrine reuptake inhibitors (SNRI) exposure on development as reflected in children's ability to meet age-appropriate developmental expectations in kindergarten, using the Early Development Instrument (EDI). We address limitations in previous studies by using a generalizable, population-based sample, conducting long-term follow-up, using a globally accepted measure of child development and a high-dimensional propensity score (HDPS) algorithm to control for confounding. To address confounding by indication, we included a comparison group of offspring of women who were diagnosed with a mood or anxiety disorder during pregnancy but did not take SSRIs or SNRIs.

METHODS

Setting and Data

We used deidentified administrative data from Manitoba, Canada (population of ~1.3 million). Data were accessed from the Manitoba Population Research Data Repository, housed at the Manitoba Centre for Health Policy (MCHP). The repository includes 99% of Manitobans and contains individual-level data on all contacts with the health care system.[31] Data are linkable across domains (ie, health, social, education) and within families, allowing for robust epidemiological research. Linkages are completed by using scrambled deidentified personal health information numbers. These data have been widely used for health services research.[32–40]

Medication use was obtained by using data from the Drug Program Information Network, which contains information on all prescription medications dispensed in Manitoba. Health data were accessed by using hospital discharge abstracts and physician claims for services provided to give counts and diagnostic information for outpatient visits. Hospital discharge abstracts are coded by using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) (before April 1, 2004)[41] and *International Classification of Diseases, 10th Revision, with Canadian Enhancement* (ICD-10-CA) (after April 1, 2004),[42] and physician claims are coded by using the ICD-9-CM.

Kindergarten assessment data were obtained from the provincial department of education.

Study Cohort

This study included all mother-child dyads for mothers with a live hospital birth between April 1, 1996, and March 31, 2014 (with follow-up until 2015), in Manitoba. Dyads were excluded for the following factors: there was no continuous health coverage of mothers from 90 days before conception to birth; there was no linkage between the mother and child, or the child was linked to >1 mother; the infant was stillborn or a multiple; the infant did not have a recorded

gestational age; the mother did not have at least 1 diagnosis of a mood or anxiety disorder from 90 days before conception, had only 1 filled SSRI or SNRI prescription, had a prescription for an antidepressant other than SSRIs or SNRIs during pregnancy, or was exposed to antipsychotics, benzodiazepines, or opioids during pregnancy. From eligible mother-child dyads, those with children with no recorded EDI were removed (Fig 1: cohort formation). The final cohort was subdivided for each EDI outcome on the basis of the availability of complete EDI records.

Exposures

Prenatal Mood or Anxiety Disorder

Mothers were considered to have a prenatal mood or anxiety disorder if in the 90 days before conception they had one of the following: 2 or more physician visits with a diagnosis for anxiety disorders; 1 or more physician visits with a diagnosis for depressive disorder, affective psychoses, or adjustment reaction; 1 or more hospitalizations with a diagnosis for anxiety disorders, anxiety states, phobic disorders, or obsessive-compulsive disorders; or 1 or more hospitalizations with a diagnosis for depressive disorder, affective psychoses, neurotic depression, or adjustment reaction. Specific ICD-9-CM and ICD-10-CA codes are listed in Supplemental Table 4.

Prenatal SSRI or SNRI

Dyads that include a mother with at least 2 prescriptions filled for SSRIs or SNRIs from the time of conception to birth were included in the prenatal SSRI or SNRI exposed group. The unexposed group included dyads with mothers who had no recorded prescriptions for antidepressants during pregnancy.

Outcome Measure

We used the EDI to measure the impact of in utero antidepressant medications on developmental outcomes among children whose mother had a diagnosis of mood or anxiety disorder. The EDI is a 104-component kindergarten teacher-completed questionnaire that measures developmental health in 5 domains: physical health and well-being, language and cognitive development, social competence, emotional maturity, and communication skills and general knowledge.[43] Children are considered developmentally vulnerable in a domain if they score in the bottom 10th percentile on the basis of national norms. Children with completed assessments accessible in the repository were included in the outcome analysis. The EDI is administered every 2 years to all students enrolled in the public school system in the second half of kindergarten (mean age of 5.7 years). The first province-wide administration of the EDI was in the 2005–2006 school year. The validity and reliability of the EDI has been reported widely, and it is used globally as a population-level indicator of developmental health.[44–48]

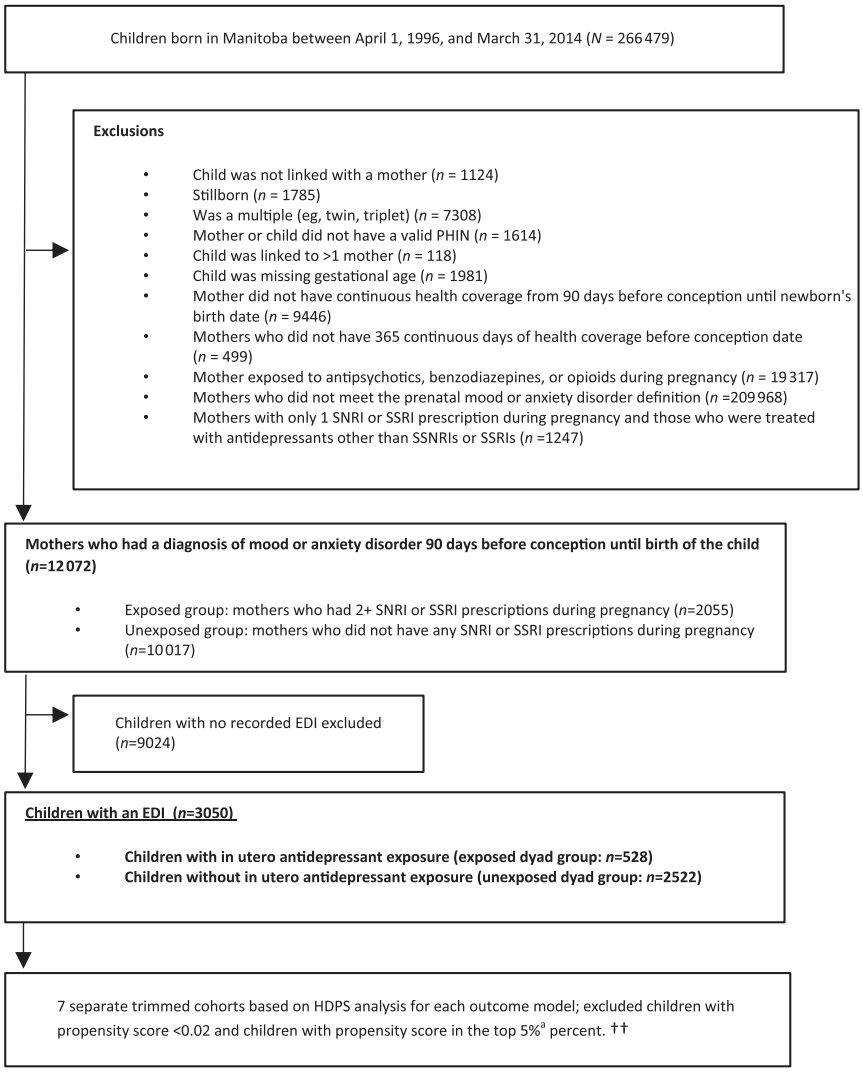

FIGURE 1
Study cohort flow diagram. PHIN, personal health information number. [a] Table 3 contains individual outcome cohort sample sizes.

Statistical Analysis

Women diagnosed with a mood or anxiety disorder who continue their medications during pregnancy may be different in health characteristics and disease severity than women who discontinue antidepressants during pregnancy. These differences may contribute to variation in outcomes seen in children versus the effect of the medications in utero. To make the 2 study groups more comparable, we used HDPS adjustments to balance differences between groups. In studies, authors have found that adjustments using HDPS have resulted in effect estimates closer to randomized control trials when compared to standard covariate adjustments.[49,50] For each of the educational outcomes, we ran HDPS adjustments using a multistep algorithm that identifies potential confounders from the database by selecting variables correlated to both the exposure and the outcome, prioritizing these covariates by prevalence and potential for bias, and integrating them into a logistic model from which propensity scores are derived.

Covariates were drawn from data 365 days before conception, which included (1) medical service tariff codes, (2) physician diagnostic codes, (3) hospital procedure codes, (4) hospital diagnostic codes, and (5) prescription medication claims. Using information from these data dimensions improves control for confounding by using numerous proxy covariates that describe the health status of women in this study, including comorbid conditions, concurrent medication use, and disease severity.

Inverse probability of treatment weights (IPTW) was applied to the data to adjust for the top 500 covariates identified in the HDPS estimation risk estimates. Using IPTW will provide a true average treatment effect of the use of SSRIs or SNRIs among depressed women. Using another method, such as matching, would produce an estimate of the treatment effect among the treated, which does not address the potential benefit or harm of expanded use of SSRIs or SNRIs in this population. The cohort was trimmed to include only those dyads with a propensity score >0.2 and less the propensity score of the 80th percentile among the treated group, to establish comparability between exposed and unexposed groups.[51] Specifically, to ensure that women from the low-propensity strata, which are primarily composed of patients for whom most physicians would regard treatment with antidepressants as inappropriate, are removed from the analyses. We calculated standardized differences for the covariates used in the HDPS model to investigate if the adjustment reduced the difference between groups. In Fig 2, we illustrate the standardized differences before and after inverse probability of treatment weighting between women unexposed and exposed to antidepressants during pregnancy and the example outcome of EDI not ready in 2 more domains. Standardized differences <0.10 were not considered clinically meaningful.

Logistic regression analyses were used for all outcome models. Prematurity, small for gestational age, and inadequate prenatal care were included as covariates in the outcome model.

RESULTS

Our cohort included 266 479 women with a live birth between 1996 and 2014. Among these women, mothers with only 1 SSRI or SNRI prescription during pregnancy, those who were treated with an antidepressant other than an SSRI or SNRI (n = 1247), and those who did not have 1 full year of health coverage before conception date (n = 499) were excluded. Among our study cohort, 12 072 women had a diagnosis of a mood or anxiety disorder before conception.

The exposed group, mothers who had 2 or more SSRI or SNRI prescription dispensations during pregnancy, included 2055 women; the unexposed group, those who did not have an SSRI or SNRI prescription during pregnancy included 10 017 women (see Fig 1). Among this cohort, 3050 children had an EDI record.

Mothers and children in the exposure groups had different levels of baseline characteristics (see Table 1). By using HDPS, each characteristic was weighted for both groups, and standardized differences were adjusted to <0.10 with a few exceptions (see Table 2, Supplemental Tables 5 through 10). The variables included in the HDPS differed for each model because they were selected on the basis of correlations to the exposure and each different educational outcome. Therefore, mothers received different weights for each outcome, resulting in a slightly different sample size for each of the outcomes presented. After trimming of each sample, exposed and unexposed dyads did not differ significantly on observed health and social covariates (see Supplemental Tables 5 through 10 for weighted and unweighted standardized differences of the top covariates in each outcome model).

Compared with children in the unexposed group, children whose mothers were dispensed at least 2 prescriptions for an SSRI or SNRI during pregnancy were at an increased risk for having developmental vulnerability in 2 or more domains measured by EDI (adjusted odds ratio = 1.43; 95% confidence interval 1.08–1.90; Table 3). Exposure to at least 2 SSRIs or SNRIs in utero was also significantly associated with being vulnerable in the domain of language and cognitive development (adjusted

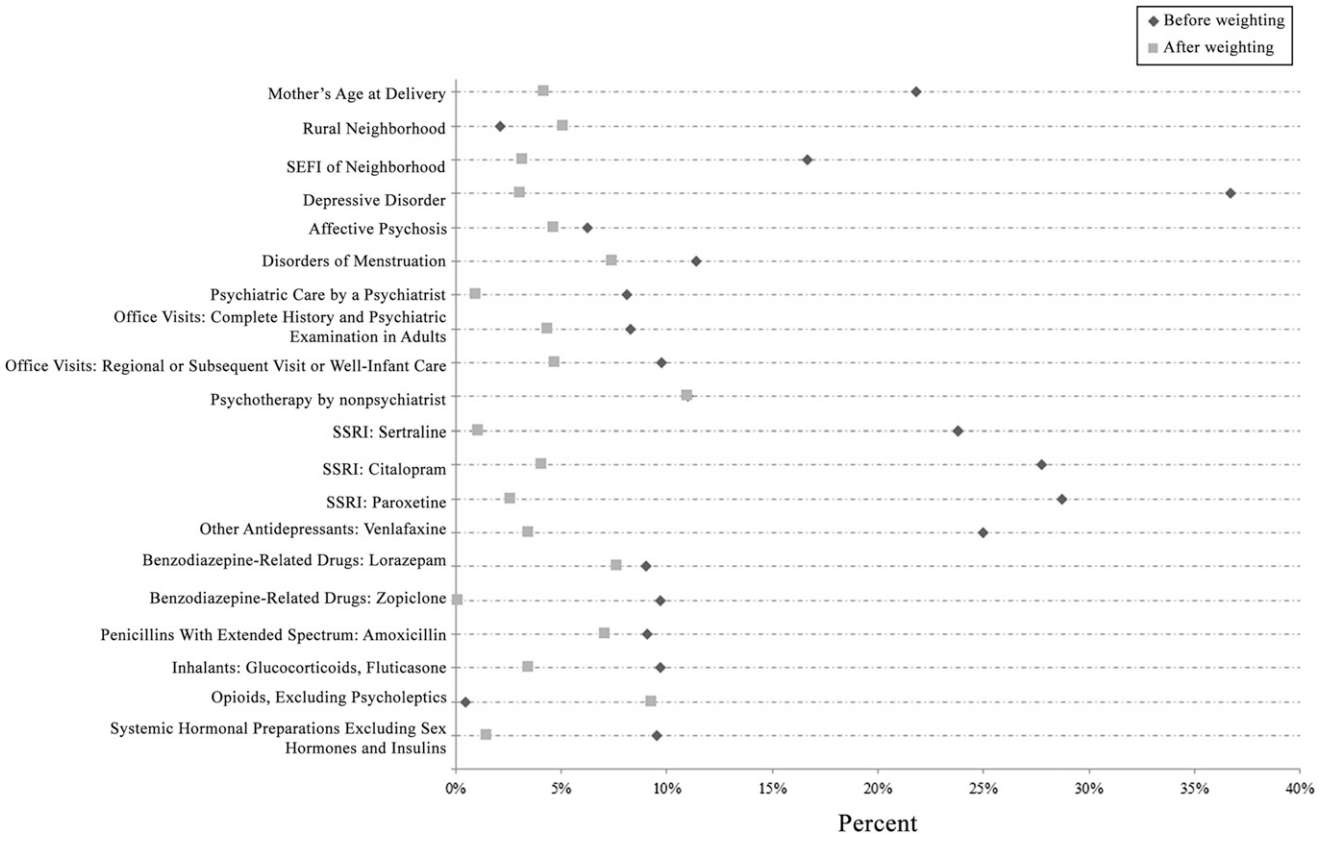

FIGURE 2

Standardized difference between women unexposed and exposed to antidepressants during pregnancy for EDI not ready in 2 or more domains. SEFI, Socioeconomic Factor Index.

odds ratio = 1.40; 95% confidence interval 1.03–1.91; Table 3). Prenatal use of 2 or more SSRIs or SNRIs were not significantly associated with developmental vulnerability in children in the following domains: physical well-being, communication and/or general knowledge, social competence, and emotional maturity, as well as 1 or more domains (Table 3).

DISCUSSION

We found 21.43% of children exposed in utero to SSRIs or SNRIs were at increased risk of being developmentally vulnerable in 2 or more domains (versus 16.16% of unexposed children), which is an absolute risk difference of 5.27%. This means for every 19 women who took an antidepressant during pregnancy in our study, 1 more child was at risk for vulnerability in 2 or more domains on the EDI. Data collection across Canada reveals that 25% or more kindergarten children are vulnerable in at least 1 area of development.[52] The percentage of children who were vulnerable in 2 or more domains is a more sensitive measure of developmental vulnerability. We also found that ~13% of children in the exposed group were vulnerable in the language and cognitive domain compared with 12% of unexposed children (absolute risk difference of 0.54%). This means, on average, 185 women would have to take an SSRI or SNRI during pregnancy for 1 more child to be vulnerable in language and cognition.

SSRI exposure on associations found in this study has biological plausibility because animal studies support that atypical serotonergic signaling resulting from prenatal SSRI exposure may alter fetal brain development.[19,53,54] Moreover, authors of a recent human study using MRI found prenatal SSRI exposure has a significant association with fetal brain development.[55]

Our findings are consistent with Johnson et al[30] (2016) who conducted an observational longitudinal study in a US clinic setting and found a significant relationship between language skills and cognitive functions with prenatal SSRI exposure. However, our findings are inconsistent with results from adjusted analyses from Kragholm et al[29] (2018) which found no association between in utero exposure to SSRIs and delayed elementary school entry and special school needs in children.

TABLE 1 Maternal, Child, and Medication Use Characteristics of Eligible Mothers With EDI Records of Children

Characteristic	Exposed Group	Unexposed Group
Total dyads, *n* (%)	528 (100.00)	2522 (100.00)
Maternal age at birth of the index child, *n* (%)	29.39 (5.57)	27.82 (5.93)
19	22 (4.17)	226 (8.96)
20–29	237 (44.89)	1315 (52.14)
30–39	253 (47.92)	916 (36.32)
40	16 (3.03)	65 (2.58)
Place of residence, *n* (%)		
Urban	358 (67.80)	1740 (68.99)
Rural	170 (32.20)	782 (31.01)
Socioeconomic status of mother at birth, mean (SD)		
SEFI-2	−0.08 (0.92)	0.10 (0.93)
Average age of child at time of EDI, mo, mean (SD)	75.05 (5.24)	74.81 (5.17)
Offspring sex, *n* (%)		
Male	274 (51.89)	1298 (51.47)
Female	254 (48.11)	1224 (48.53)
Gestational age, mean (SD)		
Gestational age	38.99 (1.61)	39.11 (1.74)
Exposure duration of medication, mean (SD)		
No. d	180.60 (100.90)	—
Trimester exposure, *n* (%)		
First trimester	456 (86.36)	—
Second trimester	372 (70.46)	—
Third trimester	400 (75.76)	—
First trimester only	93 (17.61)	—
Second trimester only	[a]	—
Third trimester only	[a]	—
First and second trimester only	30 (5.68)	—
First and third trimester only	38 (7.20)	—
Second and third trimester only	42 (7.96)	—
First, second, and third trimesters	295 (55.87)	—
Type of serotonergic antidepressant, *n* (%)		
Any SSRI	411 (77.84)	—
Fluoxetine	75 (14.21)	—
Citalopram	118 (22.35)	—
Paroxetine	128 (24.24)	—
Sertraline	98 (18.56)	—
Fluvoxamine	[a]	—
Escitalopram	[a]	—
Any SNRI	137 (25.95)	—
Venlafaxine	136 (25.76)	—
Duloxetine	[a]	—
Desvenlafaxine	[a]	—
Mood or anxiety disorder (in y before conception date)	424 (80.30)	1251 (49.60)

SEFI-2, Socioeconomic Factor Index Version 2; —, not applicable.

[a] To adhere to MCHP privacy guidelines, counts 5 and under are suppressed.

Our results add to an emerging body of literature that reveals an association of negative academic outcomes in early childhood and language difficulties for children whose mothers have a clinical indication of a mood or anxiety disorder during pregnancy who have been treated with antidepressants. Additional research using population-based samples and robust methodology are required to triangulate findings before definitive clinical recommendations can be made. Results of our study are most generalizable to women with a diagnosis of a mood or anxiety disorder before pregnancy because this is the population in which the clinical decision to continue medications during pregnancy is most relevant. Women must weigh the risks of untreated depression with their physicians before making a decision to stop taking antidepressants during pregnancy.

Our findings point to the need for early intervention and supports for children of mothers who have depression and/or anxiety disorders during pregnancy. Developmental vulnerability as measured by the EDI is considered an important measure that is associated with later positive educational outcomes,[56,57] and EDI results are a strong predictor of future academic success.[58] Brinkman et al[59] report that children with scores in the bottom 10th percentile of the EDI later test just as poorly on national standardized tests of literacy and numeracy in grades 3, 5, and 7, with the strongest correlations found within the language and cognition domain. Our findings point to the increased vulnerability in the area of language and cognition among children exposed to in utero maternal depression, highlighting the risk these children have for negative educational outcomes in the future.

This study has several strengths. First, the use of the Manitoba Population Research Data Repository provides a population-based cohort, minimizes attrition and detection bias, and allows inclusion of numerous covariates over many years. These longitudinal data are ideal for investigating outcomes during early childhood. Moreover, the use of standardized Canadian education data and a recognized global measure of educational attainment strengthens the generalizability of results. We used sophisticated design and analysis to address a frequent critique of investigations examining outcomes of children exposed to in utero antidepressant medication, namely, the ability to determine if results are confounded by the underlying maternal depression that resulted in the exposure to medication. Our use of a restricted study population of all women diagnosed with a mood or

TABLE 2 Characteristics of and Standardized Differences Between Women Unexposed and Exposed to Antidepressants During Pregnancy for EDI Not Ready in 2 or More Domains

	Before IPTW Applied			After IPTW Applied: Standardized Difference
	Unexposed (n = 2197)	Exposed (n = 392)	Standardized Difference	
	n (%) or Mean (SD)	n (%) or Mean (SD)		
Forced variables				
Maternal characteristics				
Mother's age at delivery	27.93 (5.93)	29.19 (5.59)	0.21793	0.04185
Rural neighborhood	690 (31.41)	127 (32.40)	0.02127	0.05116
SEFI[a] of neighborhood	0.08 (0.92)	−0.07 (0.90)	0.16657	0.03196
Frequency of diagnosis in the year before the conception of child				
Depressive disorder	113 (5.14)	64 (16.33)	0.36730	0.03062
Affective psychosis	23 (1.05)	7 (1.79)	0.06256	0.04668
Disorders of menstruation and other bleeding	160 (7.28)	18 (4.59)	0.11405	0.07452
Frequency of health services use in the year before conception of child				
Psychiatric care by a psychiatrist	15 (0.68)	6 (1.53)	0.08111	0.00950
Office visits: complete history and psychiatric examination in adults	35 (1.59)	11 (2.81)	0.08278	0.04390
Office visits: regional or subsequent visit or well-infant care	287 (13.06)	39 (9.95)	0.09771	0.04705
Psychotherapy by nonpsychiatrist	166 (7.56)	42 (10.71)	0.10980	0.11009
Frequency of dispensations in the year before conception of child				
SSRI: sertraline	17 (0.77)	18 (4.59)	0.23796	0.01060
SSRI: citalopram	17 (0.77)	22 (5.61)	0.27785	0.04113
SSRI: paroxetine	17 (0.77)	23 (5.87)	0.28720	0.02623
Other antidepressants: venlafaxine	9 (0.41)	16 (4.08)	0.24976	0.03460
Benzodiazepine-related drugs: lorazepam	50 (2.28)	15 (3.83)	0.09025	0.07633
Benzodiazepine-related drugs: zopiclone	12 (0.55)	6 (1.53)	0.09722	0.00097
Penicillins with extended spectrum: amoxicillin	113 (5.14)	13 (3.32)	0.09087	0.07063
Inhalants: glucocorticoids; fluticasone	12 (0.55)	6 (1.53)	0.09722	0.03484
Analgesics: opioids, natural opium alkaloids, codeine, combinations excluding psycholeptics	71 (3.23)	13 (3.32)	0.00476	0.09292
Systemic hormonal preparations (excluding sex hormones and insulins), thyroid hormones, levothyroxine sodium	16 (0.73)	7 (1.79)	0.09502	0.01483

SEFI, Socioeconomic Factor Index.

[a] A higher SEFI score corresponds with lower neighborhood socioeconomic status.

anxiety disorder decreases this confounding by indication and takes account of the difference in postnatal interactions of a mother who may be depressed versus a mother who is not depressed. The use of HDPS adjustments to balance baseline covariates adjusts for disease severity and important maternal comorbidity. The HDPS algorithm accounts for all physician and hospital visits (number of visits to physician or hospital, including number of previous suicide attempts), diagnoses (all diagnoses of mood or anxiety disorders, all diagnosis of other mental disorders, or comorbid physical disorders), and procedures, as well as all prescription medications (all medications with and without psychiatric indication) dispensed to our study population. This powerful algorithm adjusts for all measured confounders present in these data; adjustments using HDPS result in effect estimates closer to randomized control trial findings when compared to standard covariate adjustments. Moreover, HDPS has also been shown to adjust for hidden confounders,[60] supporting that this method can adjust for some unmeasured confounders as well, strengthening the robustness of our analyses.

Despite the many strengths, there are important limitations. First, there is the potential for misclassification of exposure if prescriptions were filled but not used, creating a bias toward the null. To decrease this error, we included women who had 2 or more dispensations throughout their pregnancy. Furthermore, despite using sophisticated methods to control for confounding, we cannot account for all unmeasured or residual confounding, including disease severity. It is also important to note that although the EDI is administered across the entire public school system in Manitoba, children enrolled in some schools operated by indigenous communities and private schools are not included. Furthermore, the EDI is a community-level indicator and may lack the specific diagnostic ability to identify individual neurocognitive deficits in

TABLE 3 EDI Not-Ready Results: Exposed Versus Unexposed

Not-Ready Outcomes	Exposed, *n* (%)	Unexposed, *n* (%)	χ^2	Unweighted OR (95% CI)	Weighted OR (95% CI)
1 or more domains[a]	125 (32.30)	636 (29.09)	1.82 (*P* = .17)	1.20 (0.95, 1.52)	1.20 (0.94, 1.54)
Exposed = 387, unexposed = 2202	—	—	—	—	—
2 or more domains[a]	84 (21.43)	355 (16.16)	6.56 (*P* = .01)	1.42 (1.09, 1.85)	1.43 (1.08, 1.90)
Exposed = 392, unexposed = 2197	—	—	—	—	—
Language and/or cognitive development[a]	51 (12.94)	271 (12.4)	0.09 (*P* = .76)	1.07 (0.77, 1.47)	1.40 (1.03, 1.91)
Exposed = 394, unexposed = 2186	—	—	—	—	—
Physical well-being[a]	59 (14.68)	303 (13.89)	0.17 (*P* = .67)	1.07 (0.79, 1.45)	0.95 (0.69, 1.32)
Exposed = 402, unexposed = 2182	—	—	—	—	—
Communication/general knowledge[a]	46 (11.65)	212 (9.66)	1.47 (*P* = .23)	1.24 (0.88, 1.74)	1.26 (0.89, 1.78)
Exposed = 395, unexposed = 2194	—	—	—	—	—
Social competence[a]	59 (14.79)	271 (12.37)	1.76 (*P* = .18)	1.23 (0.90, 1.66)	1.05 (0.74, 1.47)
Exposed = 399, unexposed = 2190	—	—	—	—	—
Emotional maturity[a]	55 (14.03)	281 (12.87)	0.40 (*P* = .53)	1.11 (0.81, 1.51)	1.16 (0.84, 1.61)
Exposed = 392, unexposed = 2184	—	—	—	—	—

CI, confidence interval, OR, odds ratio; —, not applicable.

[a] Denominators for each outcome vary because of HDPS trimming of each outcome group.

individual children but can identify population-level trends. Also, there may be bias in the assessment of educational outcomes by teachers; however, it is impossible to discern if bias would systematically affect our exposed versus unexposed group because teachers were not aware of exposure status. Hence, any error resulting from this bias would be random. Finally, given the multiple tests performed, chance finding cannot be ruled out. Replication of these findings in other large population-based cohorts should be conducted to help guide clinical decision-making. Studies looking at the variation in results of different types of antidepressants, dose-response effect, and gestational timing of medication on educational outcomes are warranted.

CONCLUSIONS

Children of mothers diagnosed with a mood or anxiety disorder who used SSRIs or SNRIs during pregnancy were at risk for developmental vulnerability and for language and cognitive difficulties. Early interventions should be provided to children exposed to maternal depression during pregnancy in kindergarten to help ameliorate later educational challenges.

ACKNOWLEDGMENTS

We are indebted to Healthy Child Manitoba, Manitoba Education and Training, and Manitoba Families for the provision of data. We acknowledge the MCHP for use of data contained in the Manitoba Population Research Data Repository under project 2015/16-35 registered with the Manitoba Health Information Privacy Committee. The results and conclusions are those of the authors, and no official endorsement by the MCHP, Manitoba Health, Seniors and Active Living, or other data providers is intended or should be inferred.

ABBREVIATIONS

EDI: Early Development Instrument
HDPS: high-dimensional propensity score
ICD-9-CM: *International Classification of Diseases, Ninth Revision, Clinical Modification*
ICD-10-CA: *International Classification of Diseases, 10th Revision, with Canadian Enhancement*
IPTW: inverse probability of treatment weights
MCHP: Manitoba Centre for Health Policy
SNRI: selective serotonin norepinephrine inhibitor
SSRI: selective serotonin reuptake inhibitor

Accepted for publication Feb 11, 2020

Address correspondence to Deepa Singal, PhD, Manitoba Centre for Health Policy, Community Heath Sciencs, Max Rady College of Medicine, Rady Faculty of Health Sciences, Room 408-727 McDermot Ave. University of Manitoba, Winnipeg, MB, Canada R3E 3P5. E-mail: deepakapoorsingal@gmail.com

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by an operating grant from the Canadian Institutes of Health Research (142356).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2019-3578.

REFERENCES

1. Woody CA, Ferrari AJ, Siskind DJ, Whiteford HA, Harris MG. A systematic review and meta-regression of the prevalence and incidence of perinatal depression. *J Affect Disord*. 2017;219:86–92
2. Andrade SE, Reichman ME, Mott K, et al. Use of selective serotonin reuptake inhibitors (SSRIs) in women delivering liveborn infants and other women of child-bearing age within the U.S. Food and Drug Administration's Mini-Sentinel program. *Arch Women Ment Health*. 2016;19(6):969–977
3. Malm H, Artama M, Brown AS, et al. Infant and childhood neurodevelopmental outcomes following prenatal exposure to selective serotonin reuptake inhibitors: overview and design of a Finnish Register-Based Study (FinESSI). *BMC Psychiatry*. 2012;12:217
4. Cooper WO, Willy ME, Pont SJ, Ray WA. Increasing use of antidepressants in pregnancy. *Am J Obstet Gynecol*. 2007;196(6):544.e1-5
5. Casper RC, Fleisher BE, Lee-Ancajas JC, et al. Follow-up of children of depressed mothers exposed or not exposed to antidepressant drugs during pregnancy. *J Pediatr*. 2003;142(4):402–408
6. Nordeng H, van Gelder MMHJ, Spigset O, Koren G, Einarson A, Eberhard-Gran M. Pregnancy outcome after exposure to antidepressants and the role of maternal depression: results from the Norwegian Mother and Child Cohort Study. *J Clin Psychopharmacol*. 2012;32(2):186–194
7. Rampono J, Simmer K, Ilett KF, et al. Placental transfer of SSRI and SNRI antidepressants and effects on the neonate. *Pharmacopsychiatry*. 2009;42(3):95–100
8. Kieler H, Artama M, Engeland A, et al. Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries. *BMJ*. 2012;344:d8012
9. Reis M, Källén B. Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. *Psychol Med*. 2010;40(10):1723–1733
10. Chambers CD, Hernandez-Diaz S, Van Marter LJ, et al. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med*. 2006;354(6):579–587
11. Rahimi R, Nikfar S, Abdollahi M. Pregnancy outcomes following exposure to serotonin reuptake inhibitors: a meta-analysis of clinical trials. *Reprod Toxicol*. 2006;22(4):571–575
12. Malm H, Klaukka T, Neuvonen PJ. Risks associated with selective serotonin reuptake inhibitors in pregnancy. *Obstet Gynecol*. 2005;106(6):1289–1296
13. Simon GE, Cunningham ML, Davis RL. Outcomes of prenatal antidepressant exposure. *Am J Psychiatry*. 2002;159(12):2055–2061
14. Oberlander TF, Warburton W, Misri S, Aghajanian J, Hertzman C. Effects of timing and duration of gestational exposure to serotonin reuptake inhibitor antidepressants: population-based study. *Br J Psychiatry*. 2008;192(5):338–343
15. Austin M-P, Karatas JC, Mishra P, Christl B, Kennedy D, Oei J. Infant neurodevelopment following in utero exposure to antidepressant medication. *Acta Paediatr*. 2013;102(11):1054–1059
16. Galbally M, Lewis AJ, Buist A. Developmental outcomes of children exposed to antidepressants in pregnancy. *Aust N Z J Psychiatry*. 2011;45(5):393–399
17. Pedersen LH, Henriksen TB, Olsen J. Fetal exposure to antidepressants and normal milestone development at 6 and 19 months of age. *Pediatrics*. 2010;125(3). Available at: www.pediatrics.org/cgi/content/full/125/3/e600
18. Udechuku A, Nguyen T, Hill R, Szego K. Antidepressants in pregnancy: a systematic review. *Aust N Z J Psychiatry*. 2010;44(11):978–996
19. Hermansen TK, Melinder A. Prenatal SSRI exposure: effects on later child development. *Child Neuropsychol*. 2015;21(5):543–569
20. Brown HK, Ray JG, Wilton AS, Lunsky Y, Gomes T, Vigod SN. Association between serotonergic antidepressant use during pregnancy and autism spectrum disorder in children. *JAMA*. 2017;317(15):1544–1552
21. King BH. Association between maternal use of SSRI medications and autism in their children. *JAMA*. 2017;317(15):1568–1569
22. Rai D, Lee BK, Dalman C, Newschaffer C, Lewis G, Magnusson C. Antidepressants during pregnancy and autism in offspring: population based cohort study. *BMJ*. 2017;358:j2811
23. Gentile S. Prenatal antidepressant exposure and the risk of autism spectrum disorders in children. Are we looking at the fall of Gods? *J Affect Disord*. 2015;182:132–137
24. Clements CC, Castro VM, Blumenthal SR, et al. Prenatal antidepressant exposure is associated with risk for attention-deficit hyperactivity disorder but not autism spectrum disorder in a large health system. *Mol Psychiatry*. 2015;20(6):727–734
25. Man KKC, Chan EW, Ip P, et al. Prenatal antidepressant use and risk of attention-deficit/hyperactivity disorder in offspring: population based cohort study. *BMJ*. 2017;357:j2350
26. Boukhris T, Sheehy O, Bérard A. Antidepressant use in pregnancy and the risk of attention deficit with or without hyperactivity disorder in children. *Paediatr Perinat Epidemiol*. 2017;31(4):363–373

27. Casper RC, Gilles AA, Fleisher BE, Baran J, Enns G, Lazzeroni LC. Length of prenatal exposure to selective serotonin reuptake inhibitor (SSRI) antidepressants: effects on neonatal adaptation and psychomotor development. *Psychopharmacology (Berl)*. 2011; 217(2):211–219

28. Brown AS, Gyllenberg D, Malm H, et al. Association of selective serotonin reuptake inhibitor exposure during pregnancy with speech, scholastic, and motor disorders in offspring. *JAMA Psychiatry*. 2016;73(11): 1163–1170

29. Kragholm K, Andersen MP, Mortensen RN, et al. Exposure to selective serotonin reuptake inhibitors in utero and early elementary school outcomes. *Acta Psychiatr Scand*. 2018;137(6): 481–490

30. Johnson KC, Smith AK, Stowe ZN, Newport DJ, Brennan PA. Preschool outcomes following prenatal serotonin reuptake inhibitor exposure: differences in language and behavior, but not cognitive function. *J Clin Psychiatry*. 2016;77(2):e176–e182

31. Nickel NC, Chateau DG, Martens PJ, et al; PATHS Equity Team. Data resource profile: Pathways to Health and Social Equity for Children (PATHS Equity for Children). *Int J Epidemiol*. 2014;43(5): 1438–1449

32. Brownell MD, Roos NP, Roos LL. Monitoring health reform: a report card approach. *Soc Sci Med*. 2001;52(5): 657–670

33. Jutte DP, Roos LL, Brownell MD. Administrative record linkage as a tool for public health research. *Annu Rev Public Health*. 2011;32:91–108

34. Kozyrskyj AL, Mustard CA. Validation of an electronic, population-based prescription database. *Ann Pharmacother*. 1998;32(11):1152–1157

35. Robinson JR, Young TK, Roos LL, Gelskey DE. Estimating the burden of disease. Comparing administrative data and self-reports. *Med Care*. 1997;35(9): 932–947

36. Roos LL, Gupta S, Soodeen R-A, Jebamani L. Data quality in an information-rich environment: Canada as an example. *Can J Aging*. 2005; 24(suppl 1):153–170

37. Roos LL, Menec V, Currie RJ. Policy analysis in an information-rich environment. *Soc Sci Med*. 2004;58(11): 2231–2241

38. Roos LL, Nicol JP. A research registry: uses, development, and accuracy. *J Clin Epidemiol*. 1999;52(1):39–47

39. Roos LL Jr., Nicol JP, Cageorge SM. Using administrative data for longitudinal research: comparisons with primary data collection. *J Chronic Dis*. 1987;40(1):41–49

40. Singal D, Brownell M, Chateau D, Ruth C, Katz LY. Neonatal and childhood neurodevelopmental, health and educational outcomes of children exposed to antidepressants and maternal depression during pregnancy: protocol for a retrospective population-based cohort study using linked administrative data. *BMJ Open*. 2016; 6(11):e013293

41. Centres for Disease Control and Prevention. International classification of diseases, Ninth Revision, Clinical Modifcation (ICD-9-CM). Available at: https://www.cdc.gov/nchs/icd/icd9cm.htm

42. Centres for Disease Control and Prevention. International classification of diseases, Tenth Revision, Clinical Modifcation (ICD-10-CM). Available at: https://www.cdc.gov/nchs/icd/icd10cm.htm

43. Janus M, Offord DR. Development and psychometric properties of the Early Development Instrument (EDI): a measure of children's school readiness. *Can J Behav Sci*. 2007;39(1): 1–22

44. Forer B, Zumbo BD. Validation of multilevel constructs: validation methods and empirical findings for the EDI. *Soc Indic Res*. 2011;103(2):231–265

45. Guhn M, Gadermann A, Zumbo BD. Does the EDI measure school readiness in the same way across different groups of children? *Early Educ Dev*. 2007;18(3): 453–472

46. Guhn M, Zumbo BD, Janus M, Hertzman C. Validation theory and research for a population-level measure of children's development, wellbeing, and school readiness. *Soc Indic Res*. 2011;103(2): 183–191

47. Janus M, Brinkman SA, Duku EK. Validity and psychometric properties of the Early Development Instrument in Canada, Australia, United States, and Jamaica. *Soc Indic Res*. 2011;103(2): 283–297

48. Ip P, Li SL, Rao N, Ng SSN, Lau WWS, Chow CB. Validation study of the Chinese Early Development Instrument (CEDI). *BMC Pediatr*. 2013; 13(1):146

49. Schneeweiss S, Eddings W, Glynn RJ, Patorno E, Rassen J, Franklin JM. Variable selection for confounding adjustment in high-dimensional covariate spaces when analyzing healthcare databases. *Epidemiology*. 2017;28(2):237–248

50. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology*. 2009;20(4):512–522

51. Curtis LH, Hammill BG, Eisenstein EL. Using inverse probability-weighted estimators in comparative effectiveness analyses with observational databases. *Med Care*. 2007;45(10 suppl 2): S103–S107

52. Janus M, Brinkman S, Duku E, Hertzman C, Santos R, Sayers M, Schroeder J, Walsh C. The Early Development Instrument: A Population-based Measure for Communities A Handbook on Development, Properties, and Use. Offord Centre for Child Studies. Avilable at: http://www.manitoba.ca/healthychild/edi/edi_handbook_2007.pdf. Accessed March 30, 2020.

53. Xu Y, Sari Y, Zhou FC. Selective serotonin reuptake inhibitor disrupts organization of thalamocortical somatosensory barrels during development. *Brain Res Dev Brain Res*. 2004;150(2):151–161

54. Rebello TJ, Yu Q, Goodfellow NM, et al. Postnatal day 2 to 11 constitutes a 5-HT-sensitive period impacting adult mPFC function. *J Neurosci*. 2014;34(37): 12379–12393

55. Lugo-Candelas C, Cha J, Hong S, et al. Associations between brain structure and connectivity in infants and

exposure to selective serotonin reuptake inhibitors during pregnancy. *JAMA Pediatr*. 2018;172(6):525–533

56. Duncan GJ, Dowsett CJ, Claessens A, et al. School readiness and later achievement. *Dev Psychol*. 2007;43(6):1428–1446
57. Center on the Developing Child at Harvard University. *The Foundations of Lifelong Health Are Built in Early Childhood*. Cambridge, MA: Center on the Developing Child at Harvard University; 2010
58. Forget-Dubois N, Lemelin J-P, Boivin M, et al. Predicting early school achievement with the EDI: a longitudinal population-based study. *Early Educ Dev*. 2007;18(3):405–426
59. Brinkman S, Gregory T, Harris J, Hart B, Blackmore S, Janus M. Associations between the Early Development Instrument at age 5, and reading and numeracy skills at ages 8, 10 and 12: a prospective linked data study. *Child Indic Res*. 2013;6(4):695–708
60. Guertin JR, Rahme E, LeLorier J. Performance of the high-dimensional propensity score in adjusting for unmeasured confounders. *Eur J Clin Pharmacol*. 2016;72(12):1497–1505

In Utero Antidepressants and Neurodevelopmental Outcomes in Kindergarteners

Deepa Singal, Dan Chateau, Shannon Struck, Janelle Boram Lee, Matthew Dahl, Shelly Derksen, Laurence Y. Katz, Chelsea Ruth, Ana Hanlon-Dearman and Marni Brownell

Pediatrics 2020;145;
DOI: 10.1542/peds.2019-1157 originally published online April 27, 2020;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

In Utero Antidepressants and Neurodevelopmental Outcomes in Kindergarteners

Deepa Singal, Dan Chateau, Shannon Struck, Janelle Boram Lee, Matthew Dahl, Shelly Derksen, Laurence Y. Katz, Chelsea Ruth, Ana Hanlon-Dearman and Marni Brownell

Pediatrics 2020;145;
DOI: 10.1542/peds.2019-1157 originally published online April 27, 2020;