Original Investigation

Antidepressant Use During Pregnancy and the Risk of Autism Spectrum Disorder in Children

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IMPORTANCE The association between the use of antidepressants during gestation and the risk of autism spectrum disorder (ASD) in children is still controversial. The etiology of ASD remains unclear, although studies have implicated genetic predispositions, environmental risk factors, and maternal depression.

OBJECTIVE To examine the risk of ASD in children associated with antidepressant use during pregnancy according to trimester of exposure and taking into account maternal depression.

DESIGN, SETTING, AND PARTICIPANTS We conducted a register-based study of an ongoing population-based cohort, the Québec Pregnancy/Children Cohort, which includes data on all pregnancies and children in Québec from January 1, 1998, to December 31, 2009. A total of 145 456 singleton full-term infants born alive and whose mothers were covered by the Régie de l'assurance maladie du Québec drug plan for at least 12 months before and during pregnancy were included. Data analysis was conducted from October 1, 2014, to June 30, 2015.

EXPOSURES Antidepressant exposure during pregnancy was defined according to trimester and specific antidepressant classes.

MAIN OUTCOMES AND MEASURES Children with ASD were defined as those with at least 1 diagnosis of ASD between date of birth and last date of follow-up. Cox proportional hazards regression models were used to estimate crude and adjusted hazard ratios with 95% CIs.

RESULTS During 904 035.50 person-years of follow-up, 1054 children (0.7%) were diagnosed with ASD; boys with ASD outnumbered girls by a ratio of about 4:1. The mean (SD) age of children at the end of follow-up was 6.24 (3.19) years. Adjusting for potential confounders, use of antidepressants during the second and/or third trimester was associated with the risk of ASD (31 exposed infants; adjusted hazard ratio, 1.87; 95% CI, 1.15-3.04). Use of selective serotonin reuptake inhibitors during the second and/or third trimester was significantly associated with an increased risk of ASD (22 exposed infants; adjusted hazard ratio, 2.17; 95% CI, 1.20-3.93). The risk was persistent even after taking into account maternal history of depression (29 exposed infants; adjusted hazard ratio, 1.75; 95% CI, 1.03-2.97).

CONCLUSIONS AND RELEVANCE Use of antidepressants, specifically selective serotonin reuptake inhibitors, during the second and/or third trimester increases the risk of ASD in children, even after considering maternal depression. Further research is needed to specifically assess the risk of ASD associated with antidepressant types and dosages during pregnancy.

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Editorial

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Antidepressants (ADs) are widely used during gestation for the treatment of depression. In the United States, the prevalence of AD use during pregnancy increased from 5.7% in 1999 to 13.3% in 2003[1]; in Canada, 4.5% of pregnant women reported using ADs between 2001 and 2006.[2] However, there is continued confusion regarding the appropriate use of ADs during this critical period. Gestational exposure to ADs has been associated with an increased risk of spontaneous abortion,[3] major congenital malformations,[4] prematurity,[5,6] low birth weight,[5,6] neonatal withdrawal,[7] and pregnancy-induced hypertension.[8] Discontinuation of ADs during pregnancy in women with severe depression was associated with relapse in some studies.[9] Nevertheless, up to 20% of women who continue to use ADs during pregnancy remain depressed,[10] suggesting a lack of efficacy in some pregnant women.

Autism spectrum disorder (ASD) is a neurodevelopmental syndrome detected in early childhood and characterized by alterations in communication, language, and social interaction and by particular patterns of interests and behaviors.[11] The estimated prevalence of ASD has increased from 0.04% in 1966 to approximately 1% today[12] in the United States. Although this increase is explained mainly by widening diagnostic criteria, improved detection, and the recoding of intellectual disability in ASD,[13] environmental risk factors may also play a role. Accordingly, any factor that modifies spontaneous mutation rates (eg, parental age[14]) or affects synaptic plasticity (eg, exposure to valproic acid during pregnancy[15]), including in utero exposure to medications,[16] may result in neurodevelopmental alterations included in the autistic phenotype. Although the causes of ASD remain unknown, both genetic and environmental factors are probably involved,[16] and several risk factors, such as particular genetic variants,[17] de novo mutations,[18] maternal disease,[19] and maternal history of psychiatric disorders,[20] already have been linked with ASD.

Few studies have investigated the effect of AD use during pregnancy on the risk of ASD in children.[21-24] Although some investigators have found an increased risk of ASD with antenatal AD use,[22,24] others have suggested there is no statistically significant association.[21,23] However, studies thus far have potential limitations, such as lack of adequate adjustment for maternal psychiatric illnesses and genetic predispositions for ASD. In addition, to our knowledge, no study had sufficient power to investigate the risk of ASD for each class of ADs. Given projections that depression will be the second leading cause of death by 2020,[25] ADs are likely to remain widely used, including during pregnancy. Therefore, a better understanding of the long-term neurodevelopmental effects of ADs on children when used during gestation is a public health priority. We used province-wide administrative, hospital, and clinical registers in Québec to investigate the association between AD use during pregnancy and the risk of ASD, taking into account classes of ADs, trimester of use, and maternal psychiatric conditions.

At a Glance

- This study examines the risk of autism spectrum disorder associated with antidepressant use during pregnancy, according to trimester of exposure and taking into account maternal depression.
- We conducted a register-based cohort study using data from the Québec Pregnancy/Children Cohort.
- After adjustment for all potential confounders, use of antidepressants during the second and/or third trimester was statistically associated with an increased risk of autism spectrum disorder (31 exposed infants; adjusted hazard ratio, 1.87; 95% CI, 1.15-3.04).
- Use of selective serotonin reuptake inhibitors during the second and/or third trimester was significantly associated with an increased risk of autism spectrum disorder (adjusted hazard ratio, 2.17; 95% CI, 1.20-3.93).
- The effect was persistent even after considering maternal history of depression (adjusted hazard ratio, 1.75; 95% CI, 1.03-2.97).

Methods

Cohort

We conducted a register-based cohort study using data from an ongoing population-based cohort, the Québec Pregnancy/Children Cohort (QPC). All pregnancies that occurred between January 1, 1998, and December 31, 2009, in the province of Québec (186 165 women) were prospectively recorded in the QPC. Information about individual pregnancies was obtained from province-wide databases and linked using unique personal identifiers. The QPC was first constructed by identifying all pregnancies in the Régie de l'assurance maladie du Québec (RAMQ) and the Québec centralized hospitalization archives (MedEcho) databases. The first day of the last menstrual period (first day of gestation) was defined using data on gestational age, which was validated from patient records and results of ultrasonography.[26] Data on prospective follow-up were available from 1 year before the first day of gestation, during pregnancy, and until December 31, 2009, for mothers and their children. The data sources for this study included the medical service database (RAMQ: diagnoses, medical procedures, prescribers, and socioeconomic status of women and children), the Public Prescription Drug Insurance database of Québec (drug name, start date, dose, and duration), the hospitalization archive database (MedEcho: diagnoses and procedures), and the Québec Statistics database (patient sociodemographic data and birth weight).The data sources used and the QPC are described by Bérard and Sheehy.[27] This research project was approved by the Sainte-Justine's Hospital Ethics Committee, and the linkage between administrative databases was authorized by the Commission d'Accés à l'information du Québec. Participant data were deidentified. Data analysis was conducted from October 1, 2014, to June 30, 2015.

All full-term (≥37 weeks' gestation) singleton infants born between January 1, 1998, and December 31, 2009, and whose mothers were covered by the RAMQ drug plan for at least 12 months before and during pregnancy were included in this study. Only full-term infants were considered because the critical phase of brain development occurs in the second and third trimesters. For this study, the date of birth of each infant was defined as the date of entry in the study cohort.

Exposure

We defined AD exposure as having at least 1 prescription filled at any time during pregnancy or a prescription filled before

pregnancy that overlapped the first day of gestation. Data on prescription filling for AD were validated against medical records and maternal reports,[28] with the timing of exposure defined by the date the prescription was filled and duration of therapy. Exposure to ADs was defined according to trimester of use (≥14 weeks' gestation, first trimester; 15-26 weeks' gestation, second trimester; and ≥27 weeks' gestation, third trimester). The exposure time window of interest for ASD was the second and/or third trimester.

The following AD classes were considered: selective serotonin reuptake inhibitors (SSRIs), tricyclic ADs, monoamine oxidase inhibitors, serotonin norepinephrine reuptake inhibitors, and other ADs (eTable in the Supplement). Exposure to a single class was defined as the filling of prescriptions for only 1 AD class in the time window of interest. Use of combined AD classes was defined as the filling of prescriptions for 2 or more different AD classes. The reference category for all analyses was infants who were not exposed in utero to ADs.

Outcome and Follow-up

We identified all children with a diagnosis of ASD between birth and the end of follow-up. Autism spectrum disorder was defined as a medical service claim or hospitalization with a diagnosis of ASD (childhood autism [*International Classification of Diseases, Ninth Revision* (*ICD-9*) code 299.0 or *ICD-10* code F84.0], atypical autism [*ICD-9* code 299.0 or *ICD-10* code F84.1], Asperger syndrome [*ICD-9* code 299.8 or *ICD-10* code F84.5], other pervasive developmental disorders [*ICD-9* code 299.8 or *ICD-10* code F84.8], and pervasive developmental disorders not otherwise specified [*ICD-9* code 299.9 or *ICD-10* code F84.9]). Follow-up of children continued from birth until the date of the event (index date: ASD), death (censoring), or the end of the study period (December 31, 2009; censoring), whichever occurred first.

Covariates

Four categories of variables, including maternal sociodemographic characteristics, history of maternal psychiatric and chronic physical conditions, and infant characteristics, were considered as potential confounding variables and collected in the database. Maternal sociodemographic characteristics included age at conception (<18, 18-24, 25-34, or ≥35 years), living alone (yes or no), receipt of social assistance during pregnancy (yes or no), and educational level of 12 years or more (yes or no). Infant characteristics at cohort entry included sex and year of birth to control for potential detection bias. Since in utero exposure to ADs has been shown to be associated with low birth weight and prematurity[29] and thus is potentially in the causal pathway between gestational use of ADs and the risk of ASD, infant weight and duration of pregnancy were not used as covariates. History of maternal psychiatric conditions included affective disorders, such as depression, anxiety, or bipolar disorder (yes or no), and other psychiatric disorders (yes or no). History of maternal chronic physical conditions included chronic diabetes mellitus or gestational diabetes (yes or no) and chronic or gestational hypertension (yes or no). Psychiatric conditions, diabetes, and hypertension were identified using diagnosis codes from medical services and hospitalization in the 1 year before and during pregnancy (see eAppendix in the Supplement for diagnostic codes). The data on filled prescriptions of related medications 1 year before and during pregnancy were also used to assess other psychiatric conditions, diabetes, and hypertension (eAppendix in the Supplement).

Statistical Analysis

We first performed descriptive analyses to present the characteristics of the study population, using *t* tests for continuous variables and χ^2 tests for categorical variables. Crude and adjusted hazard ratios (HRs) with 95% CIs were calculated using Cox proportional hazards regression models. The proportional hazard assumption was evaluated for all variables included in the adjusted model by comparing estimated log-minus-log survival curves. We used multivariable models to adjust HRs for all potential confounding variables listed above, including other maternal psychiatric conditions besides affective disorders (depression, anxiety, or bipolar disorder). We performed adjusted Kaplan-Meier survival curves according to status of AD exposure, initially combining all ADs together and secondly using each class of AD separately.

We further conducted a restricted analysis in women with a history of depression using Cox proportional hazard regression models. Finally, we tested the robustness of our results by conducting sensitivity analyses in which we restricted analyses to infants with a diagnosis of ASD confirmed by a psychiatrist or a neurologist. All analyses were performed with SAS, version 9.3, software (SAS Institute Inc).

Differences were considered statistically significant if the 95% CIs did not overlap 1.0 and at $P < .05$ (2-tailed). No statistical adjustment was made for multiple testing.

Results

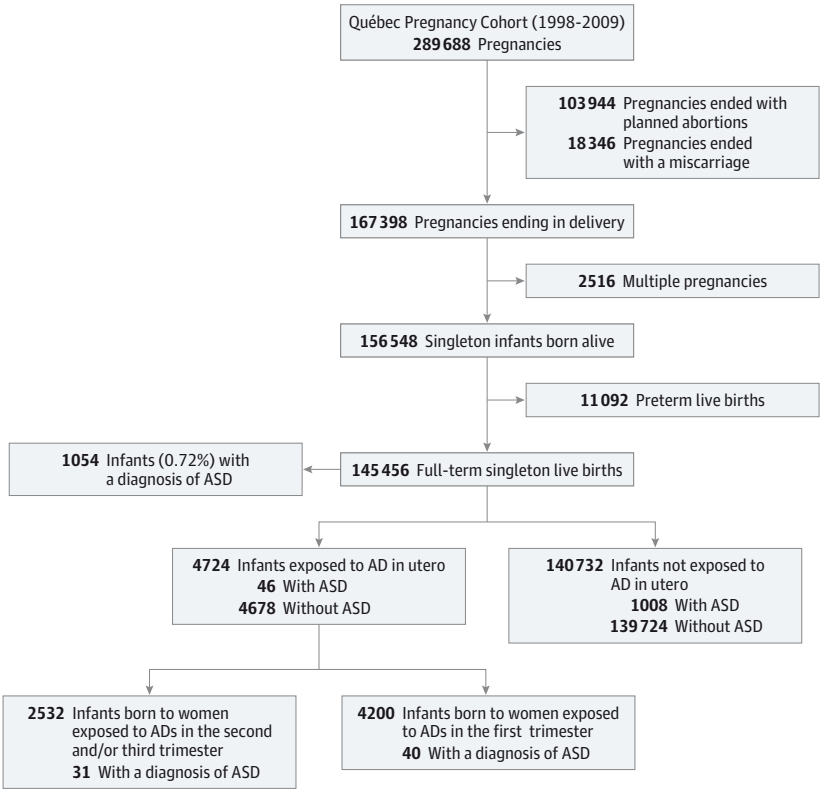
We identified 145 456 full-term singleton infants born alive, representing 904 035.50 person-years. These infants constituted the study cohort (**Figure 1**), 1054 (0.72%) of whom had at least 1 diagnosis of ASD. The mean (SD) age at first ASD diagnosis was 4.6 (2.2) years (median, 4.0 years), and the mean age of children at the end of follow-up was 6.2 (3.2) years (median, 7.0 years). Boys with ASD outnumbered girls by a ratio of about 4:1. Baseline characteristics of the study population are shown in **Table 1**. Women who used ADs during pregnancy had a higher frequency of psychiatric disorders and comorbidities than women who did not use ADs (Table 1); those using ADs were older and more likely to have had another child with ASD than those not using ADs.

Antenatal Exposure to ADs and the Risk of ASD

We identified 4724 infants (3.2%) who were exposed to ADs in utero; 4200 (88.9%) were exposed during the first trimester and 2532 (53.6%) were exposed during the second and/or third trimester. Thirty-one infants (1.2%) exposed to ADs during the second and/or third trimester and 40 (1.0%) exposed during the first trimester were diagnosed with ASD (Figure 1).

After adjustment for all potential confounders, use of ADs during the second and/or third trimester was statistically as-

Figure 1. Study Population



Flowchart of the cohort study. AD indicates antidepressant; ASD, autism spectrum disorder.

sociated with an increased risk of ASD (31 exposed infants; adjusted HR, 1.87; 95% CI, 1.15-3.04) (**Table 2** and **Figure 2**). Use of ADs in the first trimester or the year before pregnancy was not associated with the risk of ASD (Table 2).

AD Classes

Use of SSRIs during the second and/or third trimester was statistically significantly associated with an increased risk of ASD (22 exposed infants; adjusted HR, 2.17; 95% CI, 1.20-3.93), as was use of more than 1 class of AD during the second and/or third trimester (5 exposed infants; adjusted HR, 4.39; 95% CI, 1.44-13.32) (**Table 3**). Other classes of ADs were not statistically significantly associated with an increased risk of ASD (Table 3).

Assessment of Confounding by History of Maternal Depression

As a secondary analysis, we restricted our sample to children of mothers with a history of depression. Adjusting for the same potential confounders as above, use of ADs during the second and/or third trimester was also associated with an increased risk of ASD compared with those who did not use ADs (29 exposed infants; adjusted HR, 1.75; 95% CI, 1.03-2.97).

Sensitivity Analysis

We conducted the same analyses restricting the study population to children with ASD diagnoses confirmed by a psychiatrist or neurologist. We observed an increased risk of ASD associated with maternal use of ADs during the second and/or third trimester, but this risk was not statistically significant since the number of children with an ASD diagnosis was reduced by this restriction (adjusted HR, 1.65; 95% CI, 0.98-2.22).

Discussion

In this large population-based study of 145 456 children, we assessed the association between maternal use of ADs during pregnancy and the risk of ASD in children, considering timing of exposure, different AD classes, and the indication for use of ADs. This study shows that use of ADs during the second and/or third trimester is associated with an 87% increased risk of ASD, even after taking into account potential confounders; no association was observed between use of ADs during the first trimester and the risk of ASD. This increased risk was observed with the use of SSRIs only, as well as the use of more than 1 class of AD, during the second and/or third trimester. We further found that prenatal exposure to ADs during the second and/or third trimester was associated with an increased risk of ASD in children whose mothers have a history of depression.

Other studies have explored the association between use of ADs during pregnancy and the risk of ASD.[21-24,30] Taken together, these studies are suggestive of an increased risk of ASD associated with use of ADs during pregnancy. Our results on the maternal use of ADs, and of SSRIs specifically, are in

Table 1. Characteristics of the Study Cohort[a]

Characteristic	Antenatal Exposure to ADs, Value[b]				
	During Pregnancy (n = 4724)	First Trimester (n = 4200)	Second and/or Third Trimesters (n = 2532)	No Antenatal Exposure to ADs (n = 140 732)	*P* Value
Exposure to ADs 1 year before first day of gestation	3980 (84.2)	3803 (90.5)	2076 (82.0)	5227 (3.7)	<.001
Maternal characteristics					
Maternal age, mean (SD), y	28.5 (5.7)	28.6 (5.7)	28.9 (5.6)	27.8 (5.5)	<.001
<18	53 (1.1)	47 (1.1)	24 (0.9)	2864 (2.0)	
18-24	1442 (30.5)	1259 (30.0)	710 (28.0)	46 785 (33.2)	
25-34	2493 (52.8)	2221 (52.9)	1381 (54.5)	74 106 (52.7)	
≥35	736 (15.6)	673 (16.0)	417 (16.5)	16 977 (12.1)	
High school completed (≥12 y)	1635 (34.6)	1464 (34.9)	868 (34.3)	63 214 (44.9)	<.001
Living alone	1205 (25.5)	1060 (25.2)	653 (25.8)	20 468 (14.5)	<.001
Recipient of social assistance	1971 (41.7)	1768 (42.1)	1041 (41.1)	47 303 (33.6)	<.001
Infant characteristics					
Gestational age at delivery, mean (SD), wk	38.9 (1.2)	38.9 (1.2)	38.8 (1.2)	39.2 (1.2)	<.001
Male sex	2408 (51.0)	2134 (50.8)	1291 (51.0)	72 090 (51.2)	.73
Birth weight <2500 g	172 (3.6)	152 (3.6)	104 (4.1)	2752 (2.0)	<.001
Maternal psychiatric disorders in the year before or during pregnancy					
Depression, anxiety, or bipolar disorder	3290 (69.6)	2983 (71.0)	1791 (70.7)	14 651 (10.4)	<.001
Other psychiatric disorders[c]	2628 (55.6)	2374 (56.5)	1474 (58.2)	12 404 (8.8)	<.001
Maternal comorbidities in the year before or during pregnancy					
Chronic or gestational diabetes	561 (11.9)	503 (12.0)	320 (12.6)	11 882 (8.4)	<.001
Chronic or gestational hypertension	442 (9.4)	392 (9.3)	270 (10.7)	8400 (6.0)	<.001

Abbreviation: AD, antidepressant.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Compared with infants not exposed to ADs during pregnancy and calculated by Pearson χ^2 test for categorical variables and *t* test for continuous variables.

[c] Schizophrenia, schizotypal and delusional disorders, dissociative and conversion disorders, phobic disorders, obsessive-compulsive disorder, dysthymic disorder, neurasthenia, somatoform disorders, disorders of adult personality and behavior, unspecified nonpsychotic mental disorder, and drug dependence.

accordance with others. The prevalence of ASD (0.7%) in our study is consistent with the prevalence (approximately 60-110 of 10 000) published in the past 15 years.[31] The prevalence of boys with ASD in our study was higher than for girls, which again was consistent with the ratio reported in earlier epidemiologic studies.[32] Maternal age also increased the risk of ASD, as was observed in other studies.[22,24]

Several mechanisms may account for the increased risk of ASD associated with maternal use of ADs during pregnancy. Selective serotonin reuptake inhibitors cross the placenta[33] and are found in amniotic fluid.[34] Serotonin can modulate numerous prenatal and postnatal developmental processes, including cell division, neuronal migration, cell differentiation, and synaptogenesis.[35] Selective serotonin reuptake inhibitors act by blocking the serotonin transporter, which promotes the accumulation of serotonin in extracellular space. Furthermore, there is evidence that individuals with ASD have high levels of serotonin (5-hydroxytryptamine) in blood platelets,[36] termed *hyperserotonemia*. The capacity of the brain to synthesize serotonin develops atypically in children with ASD,[37] and serotonin receptor 2A binding is altered in the cerebral cortex of these individuals.[38]

Strengths of our study include the use of a well-established cohort of pregnant women with up to 11 years of follow-up, giving the advantage of a large sample size. Using the population-based QPC, we were able to obtain accurate information on filled medications, without reliance on maternal recall, for a large number of births and mothers. This database also provided accurate information about the classes of ADs used.[28] Furthermore, the length of gestation was validated by ultrasonography to determine the exact timing of in utero exposure to ADs. Physician reports were also prospectively collected, reducing the potential for detection bias, as was observed by the lack of association between calendar year of birth and the risk of ASD. To our knowledge, this is the first cohort study to examine the association between maternal use of ADs and risk of ASD in children according to trimester that takes into account maternal depression, other maternal mental disorders, and comorbidities, such as diabetes and hypertension.

Limitations of this study include the use of prescription filling data, which may not reflect actual use. However, prescription filling patterns are the most accurate data source for estimating actual medication intake in large populations.[39] Likewise, De Jong van den Berg et al[40] reported that 94% of

Table 2. Association Between Antenatal AD Exposure and the Risk of ASD

Variable	Infants, No. (N = 145 456)	Infants With Diagnosis of ASD, No. (n = 1054)	ASD Follow-up, No. of Person-Years	HR (95% CI)	
				Crude	Adjusted[a]
Exposure to ADs					
1 y Before first day of gestation	9207	82	322.69	1.35 (1.08-1.70)	1.05 (0.78-1.42)
First trimester	4200	40	145.64	1.51 (1.10-2.07)	0.84 (0.52-1.36)
Second and/or third trimester	2532	31	111.30	2.23 (1.56-3.19)	1.87 (1.15-3.04)
Infant characteristics at birth					
Male sex	74 498	836	3927.27	3.68 (3.17-4.27)	3.66 (3.15-4.25)
Calendar year	NA	NA	NA	1.08 (1.05-1.11)	1.07 (1.04-1.10)
Maternal Characteristics					
Age at the first day of gestation, y					
<18	2917	20	113.67	0.87 (0.55-1.37)	0.81 (0.52-1.29)
18-24	48 227	316	1512.04	1 [Reference]	1 [Reference]
25-34	76 599	550	2503.20	1.14 (1.00-1.31)	1.19 (1.03-1.37)
≥35	17 713	165	713.87	1.67 (1.38-2.02)	1.60 (1.32-1.94)
Marital status					
Living alone	21 673	200	911.52	1.31 (1.12-1.53)	1.24 (1.06-1.47)
High school completed (≥12 y)	64 849	446	1993.27	0.95 (0.84-1.07)	0.97 (0.85-1.11)
Recipient of social assistance	49 274	418	1963.26	1.26 (1.11-1.42)	1.22 (1.07-1.40)
Maternal psychiatric disorders in the year before or during pregnancy					
Other psychiatric disorders[b,c]	15 032	144	625.97	1.35 (1.13-1.61)	1.19 (0.98-1.44)
Maternal comorbidities in the year prior to or during pregnancy					
Chronic or gestational diabetes[d]	12 443	114	493.64	1.46 (1.20-1.78)	1.26 (1.04-1.54)
Chronic or gestational hypertension[d]	8842	96	421.23	1.71 (1.39-2.11)	1.58 (1.28-1.95)

Abbreviations: AD, antidepressant; ASD, autism spectrum disorder; HR, hazard ratio; NA, not applicable.

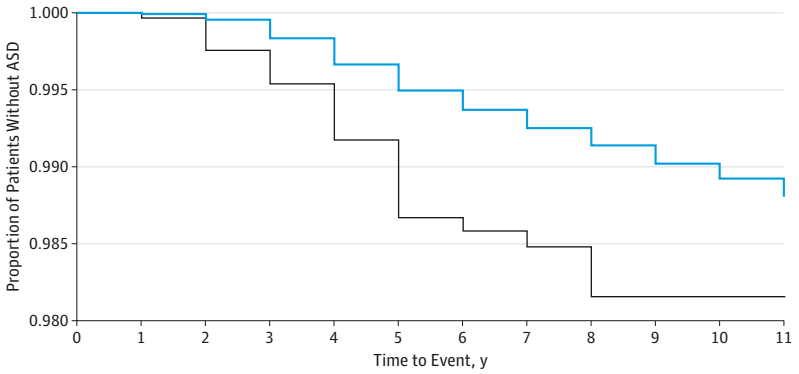
[a] Adjusted for all variables included in the table.

[b] Based on *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *ICD-10* diagnostic codes and prescriptions filled for antipsychotic medications.

[c] Schizophrenia, schizotypal and delusional disorders, dissociative and conversion disorders, phobic disorders, obsessive-compulsive disorder, dysthymic disorder, neurasthenia, somatoform disorders, disorders of adult personality and behavior, unspecified nonpsychotic mental disorder, and drug dependence.

[d] Based on *ICD-9* and *ICD-10* diagnostic codes and prescriptions filled for diabetes or hypertension medications.

Figure 2. Adjusted Kaplan-Meier Survival Curves for the Time to Diagnosis of Autism Spectrum Disorder (ASD)



No. at risk

AD use in second and/or third trimester

No	142 924	136 628	123 745	111 457	99 949	89 424	79 433	66 860	51 529	35 966	20 134	3866
Yes	2532	2346	1995	1698	1439	1182	964	750	506	302	143	26

Survival curves are stratified by exposure to antidepressants (ADs) during the second and/or third trimester.

Table 3. Association Between Exposure to Different Classes of ADs During the Second and/or Third Trimester and the Risk of ASD

Classes of ADs Used	Infants, No.	ASD Diagnosis, No.	ASD Follow-up, No. of Person-Years	HR (95% CI)	
				Crude	Adjusted[a]
Unexposed	142 924	1023	4728.25	1 [Reference]	1 [Reference]
Only SSRIs	1583	22	80.88	2.27 (1.48-3.46)	2.17 (1.20-3.93)
Only SNRIs	447	2	6.49	1.26 (0.31-5.06)	1.04 (0.20-5.46)
Only MAOIs	1	0	NA	NA	NA
Only tricyclic ADs	229	2	12.09	1.55 (0.38-6.24)	1.03 (0.23-4.61)
Other antidepressants[b]	105	0	NA	NA	NA
Combined use (≥2 AD classes)	167	5	11.73	6.09 (2.53-14.68)	4.39 (1.44-13.32)

Abbreviations: AD, antidepressant; ASD, autism spectrum disorders; HR, hazard ratio; MAOI, monoamine-oxidase inhibitor; NA, not applicable; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] Adjusted for use of ADs 1 year before the first day of gestation, use of ADs in the first trimester, infant characteristics (sex, year of birth), and maternal variables (maternal age at first day of gestation, high school completed [≥12 y], recipient of social assistance, living alone, chronic or gestational hypertension, chronic or gestational diabetes, and other psychiatric disorders).

[b] Bupropion, amoxapine, maprotiline, mirtazapine, trazodone, and nefazodone.

all drugs dispensed to pregnant women are actually taken. The QPC contained no information on maternal lifestyle, such as smoking or body mass index, which may be potential confounders. Although the association between maternal smoking and body mass index and the risk of ASD is debated, we cannot completely rule out residual confounding. Although the diagnoses of ASD in the QPC were not validated, we conducted a sensitivity analysis on children with a diagnosis of ASD confirmed by neurologists and psychiatrists. The findings of this analysis were consistent with those of the main analyses, increasing the validity of our results. Although our sample size is large, the size decreased substantially in stratified analysis on family history of ASD, which led to decreased statistical power. No adjustment was made for multiple comparisons; hence, we cannot rule out chance findings given the number of comparisons made. Our cohort comprises predominantly women and children of lower socioeconomic status insured by the RAMQ for their medications. Although this demographic can affect generalizability, it is unlikely to affect internal validity, as shown by Bérard and Lacasse.[41] Given that our findings on maternal use of ADs and the risk of ASD in children are comparable with those of other studies, external validity is likely.

Conclusions

In this large population-based cohort study, maternal use of ADs during the second and/or third trimester was associated with an increased risk of ASD. Children exposed to SSRIs alone and those exposed to more than 1 class of ADs during the second and/or third trimester had the highest risk. The effect was persistent even after taking into account maternal history of depression.

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Author Contributions: Dr Bérard and Ms Boukhris had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Boukhris, Sheehy, Bérard.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Boukhris, Bérard.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Boukhris, Sheehy,
Obtained funding: Bérard.
Administrative, technical, or material support: Bérard.
Study supervision: Bérard.

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