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Maternal Serotonergic Antidepressant Use in Pregnancy and Risk of Seizures in Children

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ABSTRACT

Objective: To evaluate whether children born to women who use serotonergic antidepressants during pregnancy have higher risk of neonatal seizures and epilepsy.

Methods: We used Swedish register-based data to examine associations between maternal-reported use of selective-serotonin reuptake inhibitor (SSRI) and selective serotonin-norepinephrine reuptake inhibitors (SNRI) in pregnancy and diagnosis of neonatal seizures and/or epilepsy in over 1.2 million children. To account for systematic differences between exposed and unexposed children we adjusted for a wide range of measured confounders. After first evaluating the role of maternal indication for SSRI/SNRI use (i.e., depression and anxiety) and parental epilepsy, we adjusted for remaining parental background factors (e.g., age, co-morbidities, education, and family socioeconomic indices) and pregnancy-specific characteristics (e.g., maternal use of other psychotropic medications and tobacco smoking in early pregnancy).

Results: Compared with all other children, children of women that reported use of SSRI/SNRI in pregnancy had an elevated risk of neonatal seizures and epilepsy (risk ratio [RR]=1.41, 95% confidence interval [CI]=1.03-1.94; hazard ratio [HR]=1.21, 95% CI=1.03-1.43 respectively). The estimates of association were attenuated by adjustment for maternal indications for SSRI/SNRI use (RR=1.30, 95% CI=0.94-1.79; HR = 1.13, 95% CI = 0.95-1.33), but not by additional adjustment for parental history of epilepsy. Full adjustment for all measured parental and pregnancy-specific factors resulted in substantial attenuation of the remaining associations (RR = 1.10, 95% CI = 0.79-1.53; HR = 0.96, 95% CI = 0.81-1.14).

Conclusions: The present study found no support for the concern that maternal SSRI/SNRI use in pregnancy increases children's risk for neonatal seizures or epilepsy.

Classification of Evidence: This study provides Class II evidence that exposure to SSRI/SNRI's in the first trimester of pregnancy is not associated with an increased incidence of neo-natal seizures/epilepsy.

INTRODUCTION

Several studies have documented an association between serotonergic antidepressant (i.e., selective-serotonin reuptake inhibitor [SSRI] and serotonin–norepinephrine reuptake inhibitor [SNRI]) use in pregnancy and neonatal seizures, particularly third-trimester use.[1-13] Few studies, however, have examined whether these medications are associated with recurrent seizures (i.e., epilepsy) in childhood.[14]

Given that seizures in neonates can be observed as part of Neonatal Abstinence Syndrome[1-13] just after antidepressant supply is cut off, it is possible that observed risks are the result of withdrawal. Prenatal exposure to serotonergic antidepressants may also disrupt synaptogenesis and neuronal growth and differentiation[14-17] in such a way that could influence the risk of longer-term, recurrent seizures.

However, before concluding that observed associations are causal, limitations to the extant literature must be addressed. Given the rarity of seizures, most previous studies have been underpowered.[1,3,4,6,8,10-13,18] More importantly, as noted in a recent review, the existing research provides correlational evidence without adjustment for important confounders, including the maternal indication for antidepressant use that could be comorbid with seizure disorders (e.g., maternal depression and anxiety).[19-22] Thus, it is unclear whether observed risks of seizures in children could be due to prenatal pharmacologic exposure or rather confounding by maternal background factors.

The present study aimed to evaluate whether children born to women who use serotonergic antidepressants during pregnancy have higher risk of neonatal seizures and epilepsy in a nation-wide sample of children. We considered many confounders not incorporated in prior studies (i.e., parental characteristics, socio-demographics, pregnancy-specific factors). We adjusted for psychiatric and behavioral health problems because there has been well-documented comorbidity between these conditions (particularly depression) and seizures that is likely to be at least partially genetic in origin.[20-22,29,30] As such, it stands to reason that parents with psychiatric and behavioral problems may be more likely to have children with seizures. We further sought to expand the previous literature by also examining the potential connection to children's risk of developing epilepsy.

METHODS

Standard protocol approvals, registrations, and patient consents

The institutional review board at Indiana University and the regional ethical review board in Stockholm, Sweden, approved this study. According to Swedish law, informed consent was not necessary because the study used data available from national Swedish registries.

Data Availability Statement

The data used in this study are national register information. The authors had no special privileges in accessing the data. Dissemination of personal information is regulated by the Swedish Secrecy Act. In accordance with Swedish law, researchers seeking access to individual-level data must apply for permission through a Research Ethics Board (etikprovningsmyndigheten.se) and from the primary owners, Statistics Sweden

(https://www.scb.se/en/services/guidance-for-researchers-and-universities), and the National Board of Health and Welfare (https://www.socialstyrelsen.se/en/statistics-and-data/statistics/).

Data source

Each individual in Sweden is assigned a unique registration number through which records of health and demographics in national registers can be linked to follow individuals over time. The present study centered on information from the Medical Birth Register, which includes data from the antenatal visits, delivery, and pediatric examination for approximately 98% of all births since 1973. Since mid-1994, women reported any use of medications as part of the standardized interview at enrolment to antenatal care, which typically occurs between weeks 8 and 12 of pregnancy.[23,24] At this time the midwife also collects information regarding the woman's age, cohabitation status, reproductive history, and use of tobacco. From mid-2005, the maternal self-report of medication use can be evaluated against the filling of prescriptions using the Swedish Prescribed Drug Register (PDR) of all filled prescriptions outside hospital.[25] Fathers were identified using the Multi-Generation Register.[26] The National Patient Register includes International Classification of Diseases (ICD) coded diagnoses made during all inpatient visits since 1987 and at outpatient specialist visits since 2001.[27] We used this register to identify parental epilepsy and psychiatric diagnoses (including depression and anxiety), as well as neonatal seizure and epilepsy diagnoses in children. Finally, we used the Integrated Database for Labor Market Research[28] and the Education Register to retrieve information on socioeconomic indices.

Sample

With register follow-up available through 2013, we followed all children born from January 1st 1996 to November 30th 2013 with respect to a diagnosis of neonatal seizures (made in the first month of life). In the evaluation of epilepsy, we required a minimum of two years follow-up, thus restricting the sample to children born before December 31st, 2011.

Measures

Exposure: We defined SSRI/SNRI exposure from the maternal self-report at enrollment to antenatal care, typically corresponding to the end of the first trimester. However, we used a cohort covered by the PDR (i.e., the n=751,887 births from mid-2006 to 2013) to show that of the women who self-reported SSRI/SNRI use during pregnancy, 64% had filled SSRI/SNRI prescriptions in the first trimester, 35% had filled SSRI/SNRI prescriptions in the second trimester, and 34% had filled SSRI/SNRI prescriptions in the third trimester. Using the same cohort, we also found the agreement between self-reported SSRI/SNRI use and second/third trimester SSRI/SNRI filled prescriptions was 98.5% (kappa = 0.63, 95% confidence interval [CI] = 0.63-0.64).

SSRIs included medications with an anatomical therapeutic chemical (ATC) code beginning with N06AB (fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram, and unspecified SSRIs). SNRIs included medications with the following ATC codes: N06AX16 (venlafaxine) and N06AX21 (duloxetine). In our cohort, 23,160 (1.49%) children were born to women who reported use of at least one SSRI or SNRI (Table 1).

Outcomes: Neonatal seizures were identified via at least one diagnosis (ICD-9 779.0 and ICD-10 P90) in the first 30 days of life.[1-13,19] Diagnosis of epilepsy (ICD-9 345 and ICD-10 G40-G41) was identified using the same sources at any time after birth.

Covariates: Covariates were identified for their ability to block potential influence from hypothesized common causes of maternal antidepressant use during pregnancy and seizure disorders in children. Pregnancy-specific characteristics included the year of birth, maternal self-report of tobacco smoking and other psychotropic medication use at the first antenatal visit. Individual parental characteristics included age and highest level of education at the time of birth and diagnosis of epilepsy, mood disorders, anxiety disorders, substance use disorder, schizophrenia, bipolar disorder, suicide attempt or record of criminal convictions prior to conception. At the family-level we considered sociodemographic factors, including parental cohabitation status, income, and a measure of neighborhood deprivation in the year of the birth. The neighborhood deprivation scores incorporated annual proportions of welfare recipients, unemployed, immigrants, divorced individuals, and individuals with low educational attainment and measures of residential mobility, crime rates, and neighborhood disposable income.[31]

Data analytic plan

We analyzed data for this study using the SAS™ software system, Version 9.4. We first performed descriptive analyses on our identified covariates, exposures, and outcomes. We then estimated associations (unadjusted and adjusted for covariates) between maternal SSRI/SNRI use in pregnancy and children's risk of seizures, using log-binomial regression for the cumulative incidence of seizures in the neonatal period and Cox proportional hazard regression for incident

diagnosis of epilepsy during follow-up. We followed children from birth to first diagnosis or censoring at time of emigration, death, or end of follow-up as the underlying time scale.

After estimating the overall associations, we adjusted for maternal indications for antidepressant use (i.e., mood and anxiety disorders) to examine the specific influence of confounding by indication. Next, we further adjusted for maternal and paternal history of epilepsy prior to conception to partially examine the potential influence of genetic confounding, given that research suggests epilepsy is heritable.[32] Finally, we estimated associations with full adjustment for all covariates, including measures of other individual parental characteristics, family socio-demographic factors and pregnancy-specific characteristics.

We conducted a sensitivity analysis to examine whether findings were susceptible to bias related to left censoring of our data, as we were not able to capture outpatient diagnoses prior to 2001. Specifically, we re-estimated associations in a cohort of children born after 2000. We also conducted a sensitivity analysis to re-estimate associations in a cohort that excluded children exposed to multiple antidepressants during pregnancy.

RESULTS

Starting out with all children born 1996-2013 (n= 1,781,353) we sequentially excluded those who were stillborn (n=6,335), had invalid maternal identifiers (n=478), were from multiple gestations (n= 52,164), had missing gestational age (n=1,101), and had missing sex (n=1), resulting in a cohort of 1,721,274 children. By further exclusion of children with missing information on the covariates of interest (n= 169,368), the complete case sample represented

90% of the target, with 1,551,906 children available for the examination of neonatal seizures and 1,367,087 children for the examination of epilepsy.

We first examined the distribution of relevant pregnancy (Table 2), maternal (Table 3), paternal (Table 4), and family-level (Table 5) characteristics in relation to maternal self-reports of SSRI/SNRIs. This information is provided for the target sample to also show the distribution of missing data, which ranged from none to approximately five percent. Women who reported use of serotonergic antidepressants in pregnancy were more likely to also report smoking and use of other psychotropic medications. Not only were psychiatric disorders and epilepsy more common among these women, they were also more common in their partners (see Table 3 and 4).

In the full analytic sample, 1.36% of women reported use of SSRIs. The most commonly reported medications were sertraline (0.49%), citalopram (0.48%), and fluoxetine (0.20%). Fewer women (0.14%) reported use of SNRIs in pregnancy, with venlafaxine being the most commonly reported medication (0.12%; Table 1).

Documented occurrence of seizures in the first month of life were rare, but more common among exposed than unexposed children (1.7 versus 1.2 per 1,000). By the age of 5 years, 5.4 per 1,000 exposed and 4.1 per 1,000 unexposed children had been diagnosed with epilepsy (Table 6).

Children born to mothers who reported use of SSRIs or SNRIs in pregnancy had 41% greater risk of experiencing seizures in the newborn period seizures (risk ratio [RR]=1.41, 95% confidence interval [CI]=1.03-1.94) and 21% greater risk of being diagnosed with epilepsy

during follow-up (hazard ratio [HR] = 1.21, 95% CI = 1.03-1.43), compared with children whose mothers did not report such use (Table 7). Adjustment for maternal indications for SSRI/SNRI use led to some attenuation of the observed associations (RR=1.30, 95% CI=0.94-1.79; HR = 1.13, 95% CI = 0.95-1.33). Further adjustment for maternal and paternal history of epilepsy had little to no influence on the estimates of association, whereas adjustment for remaining covariates greatly attenuated the remaining associations (RR = 1.10, 95% CI = 0.79-1.53; HR = 0.96, 95% CI = 0.81-1.14; Table 7).

Findings from fully adjusted sensitivity analyses on a restricted subsample of children born after 2000 suggest that our main findings were not influenced by the left censoring of our data (eTable 1). Additionally, our main findings were not impacted by the inclusion of children exposed to more than one antidepressant in pregnancy (eTable 2).

This study provides Class II evidence that exposure to SSRI/SNRI's in the first trimester of pregnancy is not associated with an increased incidence of neonatal seizures and epilepsy.

DISCUSSION

Using a large nation-wide sample, and with adjustment for a more extensive set of confounding factors than previous research,[19] we examined the risk of seizure disorders in children whose mothers reported use of SSRIs and SNRIs in pregnancy. Our evaluation of two seizure outcomes—neonatal seizures and childhood epilepsy—yielded overall reassuring results.

Consistent with prior research,[1-13] we observed a higher risk of neonatal seizures among children exposed to SSRIs/SNRIs in pregnancy, with 0.17% of exposed children affected compared with

0.12% of unexposed children. We added to prior research by showing that this association was almost entirely explained by systematic differences between the groups (i.e., maternal indications for SSRIs and SNRIs and a wide range of other pregnancy, parental, and socioeconomic factors).

We further expand on previous literature by examining the risk of epilepsy in children born to mothers reporting SSRI and SNRI use in pregnancy. Our findings are consistent with the only other study that has investigated this association,[14] as we observed an elevated risk that was entirely explained by maternal indication for SSRI and SNRI use, parental history of epilepsy, and our other covariates. Thus, we did not find evidence that maternal use of SSRI and SNRI in pregnancy increases children's risk of epilepsy.

These findings are consistent with prior evidence of shared risk for seizures and psychiatric/behavioral health conditions, particularly depression.[20-22,29,30] Research has also indicated that these comorbidities are likely to be at least partially genetically driven,[30] such that one could expect children of parents with psychiatric and behavioral health problems to have higher risk of seizures due to genetic liability. This may explain why adjustment for these factors led to attenuation of associations in our study. In fact, our findings 1) highlight the importance of adjusting for confounding by indication (i.e., depression and anxiety disorders) and other comorbidities and 2) suggest that past research may have over-estimated the risk by not adequately adjusting for confounding factors.[2,4,7-13,18]

The findings of this study are of clear clinical importance. Pregnancy is a trying time, and the addition of depression, anxiety, and other mental health conditions add to this burden. As such,

these findings may provide respite and reassurance to women (and providers) considering the risks and benefits to medication treatment, especially those who do not have the time or resources to pursue nonpharmacologic treatment. This is even more pertinent when considering the broader research literature that has observed 1) similar null findings for other adverse outcomes in children (e.g., ADHD, ASD) in relation to antidepressant use in pregnancy,[33] and 2) that untreated depression and anxiety in pregnancy is related to adverse outcomes in children.[34]

This study is subject to several limitations. Though much of the existing literature examining neonatal seizures related to antidepressant use has documented strongest associations with exposure towards the end of pregnancy[19] and suggests that exposure late in pregnancy may have important implications for longer-term neurodevelopmental outcomes,[35-37] our exposure definition was based on maternal self-reports in the first trimester. Whereas use of maternal reports could result in some misclassification of medication use, using maternal reports would also result in less misclassification than prescription records for individuals who fill prescriptions but do not use medications. We also demonstrated high agreement between maternal reports and filled prescriptions for SSRIs/SNRIs in the first as well as later trimesters of pregnancy, which is important for two reasons. First, the high concordance demonstrated in this and other studies using Swedish data suggest that maternal self-report of antidepressant use is reliable.[38,39] Second, it indicate that women reporting use in the first trimester are very likely to continue use throughout pregnancy. Nonetheless, future work should also explore the timing of exposure with comprehensive adjustment for confounding factors. In addition, we did not have detailed clinical information to identify whether a diagnosis of neonatal seizures was confirmed via EEG. While the potential for misclassification is not expected to be differential with respect to exposure (i.e.,

maternal use of SSRI in pregnancy) random misclassification could bias the estimate of association toward the null, thus hampering our ability to detect a potential small association. Our data also cannot rule out the possibility that prenatal exposure to SSRIs and/or SNRIs might pose risk in some individuals with specific co-occurring conditions (e.g., mosaic mutations in one's sodium channels). More research is needed to explore and understand any effect modification. Finally, future research is needed to understand the use of additional medications and polypharmacy in pregnancy and its relation to seizure outcomes in children.

In summary, although the present study found that children of women who use SSRIs/SNRIs are at elevated risk of neonatal seizures and epilepsy, this appears to be largely due to background factors rather than to the medication use itself.

Table 1. Exposed offspring in the complete analytic sample

	N	% of sample
SSRI/SNRI	**23160**	**1.49**
SSRI	**21104**	**1.36**
Fluoxetine	3101	0.20
Citalopram	7518	0.48
Paroxetine	1668	0.11
Sertraline	7661	0.49
Fluvoxamine	16	0.00
Escitalopram	1166	0.08
Specific SSRI unknown	142	0.01
SNRI	**2211**	**0.14**
Venlafaxine	1874	0.12
Duloxetine	340	0.02

Note: SSRI = selective serotonin reuptake inhibitor. SNRI = selective serotonin-norepinephrine reuptake inhibitor.

Table 2. Pregnancy-specific characteristics in the target sample

	SSRI/SNRI exposed n=24,308 (1.41%)	**SSRI/SNRI unexposed n=1696966 (98.59%)**
	n (%)	n (%)
Birth order		
First	11562 (47.56)	745900 (43.95)
Second	7283 (29.96)	622918 (36.71)
Third or later	5463 (22.47)	328148 (19.34)
Year of birth		
1997-1999	1162 (4.78)	248012 (14.62)
2000-2002	2647 (10.89)	259277 (15.28)
2003-2005	4172 (17.16)	281804 (16.61)
2006-2008	5322 (21.89)	299532 (17.65)
2009-2011	6735 (27.71)	314251 (18.52)
2012-2013	4052 (16.67)	203340 (11.98)
Maternal report of tobacco smoking		
None	19709 (81.08)	1463949 (86.27)
Moderate	2861 (11.77)	104381 (6.15)
High	1501 (6.17)	40383 (2.38)
Missing	*237 (0.97)*	*88253 (5.2)*
Maternal report of other medications		
Other antidepressants	509 (2.09)	2608 (0.15)
Benzodiazepines	1290 (5.31)	3137 (0.18)
Non-benzodiazepine anxiolytics	502 (2.07)	966 (0.06)
Non-benzodiazepine hypnotics/sedatives	676 (2.78)	1636 (0.1)
Antiepileptics	495 (2.04)	4672 (0.28)
Antipsychotics	408 (1.68)	3414 (0.2)
ADHD medications	129 (0.53)	403 (0.02)
Opioids	447 (1.84)	7705 (0.45)
Substance use disorder medications	56 (0.23)	484 (0.03)

Note: SSRI = selective serotonin reuptake inhibitor. SNRI = selective serotonin-norepinephrine reuptake inhibitor.

Table 3. Maternal characteristics in the target sample

	SSRI/SNRI exposed	**SSRI/SNRI unexposed**
	n=24,308 (1.41%)	**n=1696966 (98.59%)**
Epilepsy	294 (1.21)	10170 (0.6)
Mood disorder	3135 (12.9)	11624 (0.68)
Anxiety disorder	2458 (10.11)	13958 (0.82)
Substance use disorder	1320 (5.43)	16621 (0.98)
Schizophrenia or bipolar disorder	569 (2.34)	4331 (0.26)
Suicide attempts	1580 (6.5)	22418 (1.32)
Criminal convictions	2947 (12.12)	108687 (6.4)
Age at the time of the birth (years)		
Less than 20	267 (1.1)	19445 (1.15)
20-29	8822 (36.29)	698739 (41.18)
30-39	13730 (56.48)	908654 (53.55)
40 or older	1489 (6.13)	70128 (4.13)
Attained level of education		
Less than 9 years	261 (1.07)	40119 (2.36)
9 years	3564 (14.66)	155765 (9.18)
1 to 3 years upper secondary	10802 (44.44)	730715 (43.06)
Any post-secondary or postgraduate	9494 (39.06)	728410 (42.92)
Missing	*187 (0.77)*	*41957 (2.47)*
Country of origin		
Sweden	21912 (90.14)	1350737 (79.6)
Missing	*0 (0)*	*164 (0.01)*

Note: SSRI = selective serotonin reuptake inhibitor. SNRI = selective serotonin-norepinephrine reuptake inhibitor.

Table 4. Paternal characteristics in the target sample

	SSRI/SNRI exposed n=24,308 (1.41%)	SSRI/SNRI unexposed n=1696966 (98.59%)
Epilepsy	180 (0.74)	8943 (0.53)
Mood disorders	269 (1.11)	5605 (0.33)
Anxiety disorder	348 (1.43)	7677 (0.45)
Substance use disorder	854 (3.51)	21608 (1.27)
Schizophrenia or bipolar disorder	150 (0.62)	3857 (0.23)
Suicide attempts	429 (1.76)	14982 (0.88)
Criminal convictions	6443 (26.51)	335863 (19.79)
Age at the time of the birth (years)		
Less than 20	99 (0.41)	5604 (0.33)
20-29	6167 (25.37)	439033 (25.87)
30-39	13501 (55.54)	985890 (58.1)
40 or older	4197 (17.27)	246285 (14.51)
Missing	*344 (1.42)*	*20154 (1.19)*
Attained level of education		
Less than 9 years	318 (1.31)	37771 (2.23)
9 years	3013 (12.4)	179457 (10.58)
1 to 3 years upper secondary	12533 (51.56)	820735 (48.36)
Any post-secondary or postgraduate	7733 (31.81)	603014 (35.53)
Missing	*711 (2.92)*	*55989 (3.3)*
Country of origin		
Sweden	20899 (85.98)	1331796 (78.48)
Missing	347 (1.43)	20378 (1.2)

Note: SSRI = selective serotonin reuptake inhibitor. SNRI = selective serotonin-norepinephrine reuptake inhibitor.

Table 5. Family-level characteristics in the target sample

	SSRI/SNRI exposed	SSRI/SNRI unexposed
	n=24,308 (1.41%)	**n=1696966 (98.59%)**
Parental cohabitation status		
Not cohabitating	2934 (12.07)	89156 (5.25)
Missing	*279 (1.15)*	*84882 (5)*
Family income (quintile)		
1st	2088 (8.6)	113874 (6.73)
2nd	3617 (14.88)	207203 (12.21)
3rd	8008 (32.94)	515020 (30.35)
4th	7704 (31.69)	582073 (34.3)
5th	2855 (11.75)	274083 (16.15)
Missing	36 (0.15)	4713 (0.28)
Neighborhood deprivation (quintile)		
1st	3231 (13.31)	291759 (17.23)
2nd	4318 (17.76)	302476 (17.82)
3rd	4549 (18.71)	299805 (17.67)
4th	5627 (23.15)	340757 (20.08)
5th	6550 (26.95)	458175 (27)
Missing	*33 (0.14)*	*3994 (0.24)*

Note: SSRI = selective serotonin reuptake inhibitor. SNRI = selective serotonin-norepinephrine reuptake inhibitor.

Table 6. Cumulative incidence of seizures in the analytic sample

	SSRI/SNRI exposed		SSRI/SNRI unexposed	
	N events	**Events per 1,000**	**N events**	**Events per 1,000**
Neonatal Seizures	39	1.68	1825	1.19
Epilepsy diagnosis by age 5*	99	5.35 (0.547)	5325	4.08 (0.056)

Note: SSRI = selective serotonin reuptake inhibitor. SNRI = selective serotonin-norepinephrine reuptake inhibitor.

* Kaplan-Meier estimates with standard errors.

Table 7. Associations between maternal-reported SSRI and SNRI use in pregnancy and seizures in children

		Unadjusted	Adjusted for maternal indications	[b]Additionally adjusted for parental epilepsy	[c]Additionally adjusted for all other covariates
	N	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
Neonatal Seizures	1551906	1.41 (1.03, 1.94)	1.30 (0.94, 1.80)	1.30 (0.94, 1.79)	1.10 (0.79, 1.53)
	N	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Epilepsy	1367087	1.21 (1.03, 1.43)	1.13 (0.95, 1.33)	1.11 (0.93, 1.31)	0.96 (0.81, 1.14)

Note: SSRI = selective serotonin reuptake inhibitor. SNRI = selective serotonin-norepinephrine reuptake inhibitor.

RR = relative risk. HR = hazard ratio. CI = confidence interval. [a]Adjusted for maternal mood and anxiety disorders. [b]Adjusted for maternal mood and anxiety disorders and maternal and paternal epilepsy. [c]Adjusted for maternal mood and anxiety disorders; maternal and paternal epilepsy; birth order; year of birth; maternal report of tobacco smoking during pregnancy; maternal report of other medications during pregnancy (i.e., other antidepressants, benzodiazepines, non-benzodiazepine anxiolytics, non-benzodiazepine hypnotics/sedatives, antiepileptics, antipsychotics, ADHD medications, opioids, and substance use disorder medications); maternal and paternal substance use disorder, schizophrenia or bipolar disorder, suicide attempts, criminal convictions, age at the time of birth, attained level of education, and country of origin; parental cohabitation status; family income neighborhood deprivation.

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