Gestational Exposure to Selective Serotonin Reuptake Inhibitors and Offspring Psychiatric Disorders: A National Register-Based Study

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Objective: To investigate the impact of gestational exposure to selective serotonin reuptake inhibitors (SSRIs) on offspring neurodevelopment.

Method: This is a cohort study using national register data in Finland between the years 1996 and 2010. Pregnant women and their offspring were categorized into 4 groups: SSRI exposed (n = 15,729); exposed to psychiatric disorder, no antidepressants (n = 9,651); exposed to SSRIs only before pregnancy (n = 7,980); and unexposed to antidepressants and psychiatric disorders (n = 31,394). We investigated the cumulative incidence of offspring diagnoses of depression, anxiety, autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD) for the 4 groups from birth to 14 years, adjusting for confounders.

Results: The cumulative incidence of depression among offspring exposed prenatally to SSRIs was 8.2% (95% CI = 3.1–13.3%) by age 14.9 years, compared with 1.9% (95% CI = 0.9–2.9%) in the psychiatric disorder, no medication group (adjusted hazard ratio [HR] = 1.78; 95% CI = 1.12–2.82; p = .02) and to 2.8% (95% CI = 1.4–4.3%) in the SSRI discontinued group (HR = 1.84; 95% CI = 1.14–2.97; p = .01). Rates of anxiety, ASD, and ADHD diagnoses were comparable to rates in offspring of mothers with a psychiatric disorder but no medication during pregnancy. Comparing SSRI exposed to unexposed individuals, the HRs were significantly elevated for each outcome.

Conclusion: Prenatal SSRI exposure was associated with increased rates of depression diagnoses in early adolescence but not with ASD or ADHD. Until confirmed, these findings must be balanced against the substantial adverse consequences of untreated maternal depression.

Key words: SSRI, pregnancy, offspring depression, ASD, ADHD

Exposure to selective serotonin reuptake inhibitors (SSRIs) during sensitive developmental periods in rodents produces long-lasting effects on behavior, neural circuitry, morphology, and physiology.[1-3] Importantly, the developmental period during which rodents are sensitive to the effects of SSRI exposure overlaps extensively with human brain development during the fetal period. Because the serotonin (5HT) system is highly conserved across phylogeny, we suspected that similar effects might be seen in humans, as SSRIs pass readily through the placenta and enter the fetal circulation.[4] SSRIs have been prescribed increasingly to pregnant women since their introduction 30 years ago.[5,6] However, no studies have been undertaken that followed up children beyond 6 years of age for depressive disorders, which typically emerge after the onset of puberty.[7,8] Research on associations between SSRI exposure and other neurodevelopmental disorders, including autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD), has shown inconsistent results.[9-14]

The potential effect of prenatal SSRI exposure on vulnerability to later life disorders is confounded by maternal and paternal mental illness that would increase the risk of neuropsychiatric diagnoses in these children. To address these potential confounds and to better address the long-term safety of SSRI use during pregnancy for the offspring, we performed a large population-based study to investigate the effect of prenatal exposure to SSRIs, or maternal depression–related psychiatric disorders without medication, on offspring neurodevelopment through 14 years of age. Because of the steadily increasing use of SSRIs during pregnancy and the potential long-term burden of offspring depression and anxiety, this question carries substantial public health importance.

This article is discussed in an editorial by Drs. Tim F. Oberlander and Simone N. Vigod on page 351.

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METHOD

Data Sources and Study Population

We used a population-based, prospective cohort study design. All data were collected from

national registers linked by the unique personal identification number assigned to all citizens and permanent residents of Finland. In Finland, all children regularly attend child welfare clinics where trained public health nurses or physicians perform medical examinations; this is offered to all and is free of charge. These services are particularly designed to identify psychiatric and neurodevelopmental disorders. Annual examinations are performed for all school children, and, when indicated, a referral is made to specialized health care; these conditions are then recorded in the inpatient and outpatient registries. Specialized care includes hospital outpatient clinics and inpatient hospital units that are run by specialists. Psychiatric services are run by psychiatrists, who are required to have a 6-year postdoctoral specialist education. A detailed description of the registers and the study design has been published previously.[5]

The total sampling frame includes 845,345 singleton live births in Finland between January 1, 1996, and December 31, 2010. Accordingly, the age range of children in the study cohort is from birth to age 14 years. The mother–child dyads were identified from the national Medical Birth Register (MBR). The register collects data on maternal demographics, reproductive and medical history, health-related behaviors, diagnoses during pregnancy and delivery, and neonatal outcome since 1987, using the *International Classification of Diseases, 10th Revision (ICD-10)* coding since 1996.

The Drug Reimbursement Register, maintained since 1995, collects data on prescription drug purchases and was used to identify the study groups. Drug purchases are recorded concomitantly with the purchase at pharmacies using the International Anatomic-Therapeutic-Chemical (ATC) classification, and drugs are supplied for a maximum of 3 months at a time. The Special Reimbursement Register contains data on chronic illnesses requiring continuous medication since 1964.

The Hospital Discharge Register (HDR) includes inpatient diagnoses covering all somatic and psychiatric hospitals in Finland since 1969, and outpatient diagnoses in public hospitals since 1998. The diagnoses are coded using the *ICD-8* (1969–1986), *ICD-9* (1987–1995), and *ICD-10* since 1996. Information on parental psychiatric diagnoses (*ICD-8*, *ICD-9*, and *ICD-10*), and diagnoses of neuropsychiatric disorders in offspring (*ICD-10*) were derived from this register. Patients treated solely in public primary or in private care are not included in this register.

The national population register contains basic information, including country of birth, marital status, marriages and divorces, and deaths of all Finnish citizens and other citizens residing permanently in Finland.

The register administrators and the data protection authority approved the use of sensitive health registry data for scientific research and the data linkages. The Institutional Ethical Review Board at the National Institute for Health and Welfare, the Social Insurance Institution in Finland, and the institutional review board of the New York State Psychiatric Institute approved the study protocol. All data were anonymized and de-identified before analysis. The study participants were not contacted, and, according to Finnish legislation, informed consent was therefore not required.

Exposure Groups, Mother–Child Dyads

SSRI Exposed Group. Mothers in the SSRI exposed group (n = 15,729) had 1 or more purchases of SSRIs (fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram) during the period from 30 days before pregnancy until the end of pregnancy; the date of purchase indicated the beginning date for each exposure. The beginning of gestation corresponding to the last menstrual period was calculated from the best clinical estimation of gestational age at birth, primarily based on ultrasound and

MBR registration. Information on diagnosis of depression or depression-related diagnoses was available for 4,811 (30.6%) mothers in this group; that is mothers, who had been treated in inpatient care or outpatient specialized care, and accordingly had a diagnosis in the HDR. Among the mothers with diagnoses available in the register, 4,713 (98.0%) had a diagnosis related to affective disorders (depression, anxiety, bipolar disorder), and 265 (5.5%) had a diagnosis of nonaffective or undefined psychosis.

The mutually exclusive comparison cohorts included:

Psychiatric Disorder, No Medication Group (n = 9,651). The psychiatric disorder, no medication group (n = 9,651) was exposed to maternal psychiatric diagnosis but no SSRI during pregnancy. This group included all mothers who had a diagnosis of depression or other psychiatric disorder related to depression or SSRI use, obtained from the HDR (*ICD-10* F20–F48; *ICD-9* 295–298, 300) from 1 year before pregnancy until discharge (≤3 weeks) from hospital after delivery, and no purchases of antidepressants (ATC codes N06A, N06CA) or antipsychotics (N05A) from 3 months before until the end of pregnancy. In all, 9,407 mothers (97.5%) had a diagnosis related to affective disorders, and 424 (4.4%) had a diagnosis of nonaffective or undefined psychosis.

SSRI Discontinued Group. The SSRI discontinued group (n = 7,980) was exposed to SSRIs only before pregnancy. Mothers had 1 or more purchases of SSRIs during 1 year before pregnancy until 3 months before pregnancy but no purchases of antidepressant or antipsychotic drugs during 3 months before pregnancy until delivery.

Unexposed Group (n = 31,394). The unexposed group (n = 31,394) was not exposed to SSRIs and had no diagnosis of depression or other psychiatric disorder related to depression or SSRI use. This group included mothers with no purchases of antidepressants or antipsychotics, and no depression or related psychiatric disorder at any time before or during pregnancy. Two unexposed per 1 participant exposed to SSRI were matched for offspring date of birth within ±6 months.

Outcome Variables

The outcome variables included the following: depression, including depressive disorders and unspecified affective disorders (*ICD-10* F32–F39); anxiety, including anxiety disorder (F40–F41); autism spectrum disorder (ASD; F84, but excluding Rett syndrome, F84.2); and attention-deficit/hyperactivity disorder (ADHD; F90). Only *ICD* codes used after the diagnosis was established (*ICD-10* F-codes for psychiatric disorders) were included; codes used in the evaluation process (*ICD-10* Z-codes) were excluded. We excluded individuals with a depression diagnosis only during the first 2 years of life if the diagnosis was not recorded at later stages.

Covariates

Data on covariates were derived from the registers described above and are delineated in Table 1. Although the register data have high coverage for most covariates, data on socioeconomic status (SES) are recorded less accurately. The SES classification is based on maternal occupation, and nearly one-third of participants were classified as "others," including students, housewives, entrepreneurs, and those who were unemployed.

Statistical Analyses

Clinically relevant and plausible covariates were first tested (Table 1). Sex was included in all adjusted models. Because SES and maternal psychiatric disorders are associated with psychiatric drug use and child neurodevelopment, SES and maternal history of other

TABLE 1 Maternal, Neonatal, and Family Characteristics Tested as Covariates by the 4-Class Exposure Status

| Characteristic | Exposure | | | | | | | | Association of Covariate With Exposure Status |
| | SSRI Exposed n = 15,729 | | Psychiatric Disorder, No Medication n = 9,651 | | SSRI Discontinued Group n = 7,980 | | Unexposed n = 31,394 | | |
	n	%	n	%	n	%	n	%	p Value
Maternal age, y									<.0001
≦19	524	3.3	954	9.9	217	2.7	775	2.5	
20–29	7,426	47.2	4,530	46.9	3,632	45.5	15,523	49.5	
30–39	7,023	44.7	3,768	39.0	3,826	47.9	13,959	44.5	
≧40	756	4.8	399	4.1	305	3.8	1,137	3.6	
Place of residence									<.0001
Urban	10,687	68.0	6,706	69.5	5,608	70.3	21,233	67.8	
Semiurban	2,552	16.2	1,512	15.7	1,161	14.6	5,050	16.1	
Rural	2,489	15.8	1,427	14.8	1,209	15.2	5,054	16.1	
Marital status at birth									<.0001
Married or in relationship/divorced	13,364	89.6	7,918	88.1	6,940	92.4	28,832	95.5	
Socioeconomic status									<.0001
Upper white collar worker	1,857	11.8	1,219	12.6	1,207	15.1	5,360	17.1	
Lower white collar worker	4,954	31.5	2,824	29.3	2,683	33.6	10,479	33.4	
Blue collar worker	2,493	15.9	1,435	14.9	1,263	15.8	4,271	13.6	
Other[a]	3,669	23.3	2,365	24.5	1,499	18.8	5,728	18.3	
Unknown	2,756	17.5	1,808	18.7	1,328	16.6	5,556	17.7	
Parity									<.0001
No previous births	6,534	41.6	4,455	46.2	3,665	45.9	12,817	40.8	
Smoking during pregnancy	4,575	29.9	2,737	29.1	1,855	23.8	3,947	12.9	<.0001
Exposure to teratogenic[b] drugs	18	0.1	10	0.1	13	0.2	30	0.1	.44
Exposure to anxiolytics[c] and sedatives	2,933	18.7	426	4.4	329	4.1	147	0.5	<.0001
Exposure to antiepileptic[d] drugs	500	3.2	162	1.7	77	1.0	136	0.4	<.0001
Entitlement to special reimbursement for any chronic disease ever	179	1.1	126	1.3	94	1.2	230	0.7	<.0001
Preterm birth <37 wk	821	5.2	608	6.3	379	4.8	1,379	4.4	<.0001
Birth weight <2,500g	572	3.6	430	4.5	280	3.5	989	3.2	<.0001
Neonatal care unit	2,405	15.3	1,160	12.0	857	10.7	3,032	9.7	<.0001
Maternal history of other psychiatric diagnoses[e]	3,589	22.8	2,532	26.2	997	12.5	612	2.0	<.0001
Maternal history of substance abuse[f]	1,815	11.5	1,096	11.4	525	6.6	240	0.8	<.0001
Paternal history of psychiatric diagnoses[g]	3,393	21.6	2,251	23.3	1,356	17.0	2,885	9.2	<.0001
Mother's country of birth									<.0001
Other than Finland	706	4.5	591	6.1	367	4.6	4,280	13.6	
Parental death	422	2.7	243	2.5	162	2.0	261	0.8	<.0001

Note: Differences between the groups analyzed by χ^2 test and when not valid, by Fisher exact test. Percentages were calculated from nonmissing data. Missing values, n (%): place of residence, 66 (0.1); marital status, 3,158 (4.9); previous births, 20 (0.0); smoking during pregnancy, 1,629 (2.5); mother's country of birth, 1 (0.0). SSRI = selective serotonin reuptake inhibitor.

[a]For example, students, housewives, entrepreneurs, unemployed persons.

[b]Teratogenic drugs: purchases of isotretinoin (Anatomic-Therapeutic-Chemical [ATC], code D10BA), acitretin (D05BB02), antineoplastic agents (L01), methotrexate (L04AX03), mychophenolate (L04AA06), misoprostol (A02BB01 and M01AB55), carbimazole (H03BB01) any time during pregnancy or 1 month before pregnancy.

[c]Anxiolytics and sedatives: purchases (ATC codes N05B, N05C) any time during pregnancy or 1 month before pregnancy.

[d]Antiepileptic drugs: purchases (ATC code N03) any time during pregnancy or 1 month before pregnancy.

[e]Maternal history of other psychiatric diagnoses: any other psychiatric diagnosis than depression-related disorders (F20–F48 used as inclusion/exclusion criteria) or substance abuse (International Classification of Diseases 10th Revision [ICD-10] F50–F99; 9th Revision [ICD-9] 299, 301–302, 307, 309, 312–319; 8th Revision [ICD-8] 301, 302.10–302.99, 305–308, 310–315), recorded ever before delivery.

[f]Maternal history of substance abuse: (ICD-10) F10–F19; (ICD-9) 291, 292, 303, 304, 305; (ICD-8) 291, 294.30, 303, 304, ever recorded.

[g]Paternal history of psychiatric diagnoses: (ICD-10) F10–F99; (ICD-9) 291–292, 295–309, 312–319; (ICD-8) 291, 294.30, 295–301, 302.10–308, 310–315, ever recorded.

psychiatric diagnoses (excluding depression-related disorders, which were used in defining 1 comparison group, and substance abuse; see Table 1 for *ICD* codes) were further included in all adjusted analyses. Other covariates were included in the models if they were associated with both exposure and outcome at $p < .1$.

To take into account the fact that children born between 1996 and 2010 were aged 0 to 14 years at the end of the follow-up in 2010, we used survival methods. Events in the survival analysis were defined as age at the first diagnosis of the studied outcome. Separate survival analyses were conducted for each of the 4 outcomes. Time observations after migrating, dying, and the end of the follow-up on December 31, 2010 were censored. We plotted the cumulative incidence of offspring diagnoses among the SSRI exposed, the psychiatric disorder, no medication group, the SSRI discontinued group, and the unexposed group using the Kaplan–Meier method. To compare offspring psychiatric diagnoses among these 4 groups, Cox proportional hazards models were used. Data from siblings in the same family were treated as clusters because outcomes from the same family are likely to be related. Robust sandwich estimates of the variance of the estimated Cox regression parameters were used for this purpose. Each outcome was analyzed separately by fitting 2 models: a crude model adjusted only for sex, and a model adjusted for additional covariates associated with the exposure and each specific outcome. The "unknown" category for SES was included, as the missing observations occurred completely at random. The age-specific depression and anxiety rates in offspring by different exposure groups were estimated with a Poisson-regression model, assuming a Poisson error distribution. All analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Maternal and family characteristics tested as covariates by exposure status are shown in Table 1, tested by offspring outcome diagnosis in Table S1 (available online), and specifically for offspring depression in Table S2 (available online). The distribution of offspring by birth year demonstrates that in the SSRI exposed group, fewer offspring were in the oldest age cohort (1.6%) compared to offspring in the psychiatric disorder, no medication group (2.3%), or the SSRI discontinued group (3.4%) (Table S3, available online). The person-years under observation in each of the offspring groups are presented in Table S4 (available online). The number and percentage of offspring who migrated or died according to exposure group in different age groups are shown in Table S5 (available online).

Children exposed to SSRIs during gestation were diagnosed with depression increasingly from age 12 onward compared to the control groups that were not exposed, reaching a cumulative incidence of 8.2% by age 14.9 years, compared with 1.9% in the psychiatric disorder, no medication group, 2.8% in the SSRI discontinued group, and 1.6% in the unexposed group (Figure 1A, Table 2; Figure S2, available online). The adjusted hazard ratio (HR) for depression in offspring exposed to SSRIs was 1.78 (95% CI = 1.12–2.82; $p = .02$) compared with the psychiatric disorder, no medication group and 1.84 (95% CI = 1.14–2.97; $p = .01$) compared with the SSRI discontinued group (Figure 2A, 2B; Table S6, available online). The age-specific incidence rate per 10,000 person-years of offspring depression in the oldest age group, 12 to 14 years, was 180.7 in the SSRI exposed group compared to 35.1 in the psychiatric disorder, no

medication group, 84.8 in the SSRI discontinued group, and 58.4 in the unexposed group (Table S7, available online). We tested for sex interaction, and there was no significant interaction in comparisons between the main exposure groups (SSRI exposed group; psychiatric diagnosis, no medication group; SSRI discontinued group) and depression.

Although gestational SSRI exposure was associated with higher rates of depression in adolescent offspring, there was no increase in diagnosed anxiety disorders (Figure 1B, Figure 2; Table S6, available online). Likewise, the age-specific incidence rate of anxiety in the oldest age group differed only marginally between the SSRI exposed, the psychiatric disorder, no medication, and the SSRI discontinued groups (Figure 1B; Table S8, available online). Rates of ASD and ADHD diagnoses in the SSRI exposed group were comparable to rates in offspring of mothers with a psychiatric disorder who did not use SSRIs during pregnancy, and to rates in offspring of mothers who discontinued SSRIs before pregnancy (Figure 1C, 1D, Figure 2; Table S6, available online). The age-specific incidence rates of ASD and ADHD are presented in Tables S9 and S10 (available online). Comparing SSRI exposed to unexposed, the HRs were significantly elevated for each outcome (Table S6, available online). Although there was an increasing trend for ASD, no significant HRs were observed for any of the outcomes when comparing the psychiatric disorder, no medication group to the SSRI discontinued group, whereas comparing the psychiatric disorder, no medication group to the unexposed group, the HRs were increased for ASD and ADHD (Table S11, available online).

Restricting exposure to SSRI monotherapy (n = 12,121) still yielded increased HRs for offspring depression when compared with the psychiatric disorder, no medication group (HR = 1.85; 95% CI = 1.15–2.98; $p = .01$) and with the SSRI discontinued group (HR = 2.12; 95% CI = 1.29–3.48; $p = .003$). After adjustment for other possible indicators of maternal illness severity, including diagnoses related to suicidal behavior, the HR for offspring depression remained significantly elevated in the SSRI exposed compared with all comparison groups (Table S12, available online).

DISCUSSION

Principal Findings

Using national register data, we observed increased rates of depression emerging at 12 to 14 years in offspring exposed prenatally to SSRIs. Taking into account maternal underlying psychiatric disorder, SSRI exposure was not associated with an increased risk of ASDs, ADHD, or anxiety. This study, like all studies attempting to answer questions about the long-term effects of in utero exposure to SSRIs, was observational, as it would not be possible to carry out a clinical trial of different exposures specially looking for effects, such as depression, manifesting earliest at 12 to 14 years of age.

Strengths and Weaknesses

A major strength is that we took into account maternal underlying psychopathology. Antenatal depression itself is associated with an increased risk of emotional disorders in

FIGURE 1 Cumulative incidence (%) of offspring diagnoses by age. Note: Shown below is cumulative incidence (%) of offspring diagnoses by age among offspring born between January 1, 1996, and December 31, 2010, and followed up through December 31, 2010 (age range 0.0–14.9 years at the end of follow-up). Participants were censored from the age-defined analysis after December 31, 2010. Offspring exposed prenatally to selective serotonin reuptake inhibitors (SSRIs) are represented by magenta line, offspring exposed to maternal psychiatric disorder but no medication by cyan line, offspring of mothers discontinuing SSRI use prior to pregnancy by yellow line, and offspring unexposed to maternal psychiatric disorder and medication by black line. Panels A to D illustrate separately offspring depression (A), anxiety (B), autism spectrum disorder (ASD) (C), and attention-deficit/hyperactivity disorder (ADHD) (D).
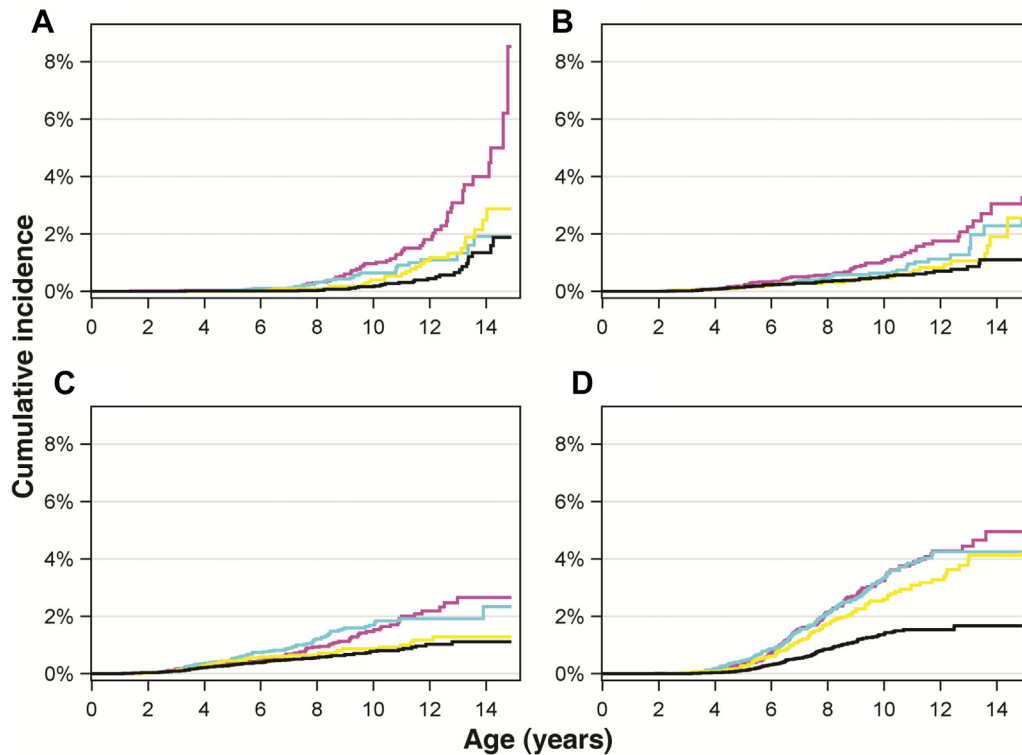
offspring,[15] suggesting by extension that maternal depression severity affects offspring risk. Hence, we controlled for potential depression severity differences between the SSRI exposed and the psychiatric diagnosis, no medication groups. Two prior studies have shown that, contrary to recommendations, the severity of maternal psychiatric symptoms is not related to the choice to continue or discontinue medication use during pregnancy,[16,17] allowing us to use the SSRI discontinued group as a depression severity control. Furthermore, we excluded women using multiple psychotropic medications (a proxy for severity) and restricted our exposure to SSRI monotherapy. This refined SSRI exposure group still yielded increased HRs for offspring depression when compared to the psychiatric disorder, no medication group and the SSRI discontinued group. After adjustment for other possible indicators of maternal illness severity, including previous diagnoses related to suicidal behavior, the HR for offspring depression remained significantly elevated in the SSRI exposed compared to all comparison groups. Hence, when both main comparison groups were adjusted for these "severity proxies," the significance of SSRI exposure as the principal variable did not diminish.

Recent studies found that increased rates of ASD associated with in utero exposure to SSRIs became nonsignificant when controlled for maternal psychiatric illness.[9,10] Our findings are in line with those results and show that, similar to ASD, SSRI exposure added no additional risk above mothers' psychiatric illness to offspring ADHD and anxiety. Yet offspring of both groups (SSRI exposed and psychiatric disorder, no medication groups) had higher risks of ASD and ADHD than offspring of mothers with no diagnosis and no psychotropic medication use. Likewise, the use of SSRI medications before pregnancy did not increase the rates of these disorders over and above the rates seen with maternal illness alone and no gestational SSRI use. We acknowledge that in this register-based setting, we cannot fully confirm the comparability of the exposure groups, but these observations support the notion that our main comparison groups (SSRI exposed, psychiatric disorder, no medication group, and SSRI discontinued group) were not biased by increased severity of illness in mothers using SSRIs during pregnancy.

A further strength is the high quality of the register data included in the study. The quality and coverage of the MBR have been validated and are considered good,[18] and the Population Register covers all Finnish citizens and permanent residents in Finland.[19] The quality of the HDR has been validated and is good for psychiatric diagnoses.[20]

TABLE 2 Cumulative Incidence and 95% CIs by Age 14 Years for Depression, Anxiety, Autism Spectrum Disorders (ASDs) and Attention-Deficit/Hyperactivity Disorders (ADHD) in Offspring of Mothers Using Selective Serotonin Reuptake Inhibitors (SSRIs) During Pregnancy, Offspring of Mothers With Psychiatric Disorder but No Antidepressant Use, Offspring of Mothers Discontinuing SSRI Use Before Pregnancy, and in Unexposed Offspring

Offspring Diagnosis	SSRI Exposed n = 15,729		Psychiatric Disorder, No Medication Exposed n = 9,651		SSRI Discontinued Group n = 7,980		Unexposed n = 31,394	
	n	Cumulative Incidence,ᵃ % (95% CI)	n	Cumulative Incidence,ᵃ % (95% CI)	n	Cumulative Incidence,ᵃ % (95% CI)	n	Cumulative Incidence,ᵃ % (95% CI)
Depression	60	8.2 (3.1—13.3)	30	1.9 (0.9—2.9)	25	2.8 (1.4—4.3)	30	1.6 (0.8—2.4)
Anxiety	65	3.1 (1.8—4.3)	39	2.3 (1.3—3.2)	27	2.6 (0.9—4.2)	62	1.1 (0.6—1.6)
ASD	88	2.7 (1.9—3.5)	79	2.3 (1.9—2.8)	40	1.3 (0.8—1.8)	100	1.1 (0.8—1.4)
ADHD	160	4.9 (3.8—6.0)	137	4.2 (3.5—5.0)	93	4.1 (3.1—5.1)	124	1.7 (1.3—2.0)

Note: Depression included depressive disorders and unspecified affective disorders (International Classification of Diseases 10th Revision [ICD-10] code: F32—F39). ICD-10 code for anxiety: F40—F41. ICD-10 code for ASD: F84 (excluding Rett syndrome, F84.2) and for ADHD: F90.
ᵃKaplan—Meier method.

Approximately 1% of children in Finland have been diagnosed in specialized services with ASD until age 14 years,[8] close to population-based estimates in western countries.[21] Therefore, it is likely that most children with ASD in the community are identified in the register. Furthermore, the diagnostic validity of Finnish register–based diagnoses of ASD is high.[22]

As we have described in detail in previous work,[5,8] children under 16 years have yearly medical check-ups in Finland; those who have serious psychiatric disorders are referred to specialized services for assessment. Therefore, it is likely that children with severe and moderate problems are found in registers. However, those with less serious problems might not be identified in medical check-ups or may not be referred to specialized services, potentially reducing the generalizability of our findings. Differential treatment seeking is also a potential limitation if children with depression in the community have different probabilities of being referred to specialized services depending on mothers' medication use. It is unlikely, however, that offspring referral to specialized services would depend on the timing of mothers' SSRI use (before or during pregnancy). The specific impact of SSRI exposure on offspring depression but not on other neuropsychiatric diagnoses also mitigates the possible confound of surveillance bias.

A limitation is that even in this large population-based sample, the numbers were too small to allow trimester-specific analyses. As in all register-based studies, a major limitation is that we cannot confirm adherence to the purchased drugs. However, noncompliance would result in overestimating exposure, likely biasing the observed associations toward null. Previous research has also indicated a good correlation between prescription register data and self-reported antidepressant use.[23] We also consider the risk of false-negative results, unexposed offspring who in fact were exposed, as minimal, because the drug imbursement register covers more than 98% of all drug purchases in Finland.[24] We had no direct information on alcohol or illicit drug use, but we controlled for substance abuse for both parents by identifying related diagnoses in the HDR. A further limitation is that we had no information about postnatal environment. Although the findings on maternal SSRI use and depression persisted adjusting for previous diagnoses related to suicidal behavior, it is possible that postnatal experiences associated with maternal SSRI use and depression may have influenced the results.

Comparison With Previous Studies

Previous studies investigating the association between prenatal exposure to SSRIs and child internalizing behavior outcomes have shown inconsistent results.[25-27] The sample sizes in those clinical studies were small, ranging from 22 to 62 children, and the follow-up time extended only until 3 to 6 years of age. In the largest sample, children exposed prenatally to SSRIs were more likely to present with internalizing problems by age 6 years than those exposed to maternal depression only, but the severity of maternal depression rather than antidepressant use predicted child behavior.[25] In the other studies, maternal anxiety and SSRI use[26] and maternal depression and anxiety only[27] were associated with an increased risk of offspring internalizing behavior. Two of the studies assessed child behavior at only 1 time point[25,26] and by maternal self-report,[26] which may have caused misclassification bias. Prior studies of prenatal SSRI exposure in relation to offspring ASD and ADHD have revealed conflicting results. In line with our results, 2 register-based studies[9,10] and a study using electronic health records[11] did not show an association between SSRIs and offspring ASD. Furthermore, a register-based study found no independent association with SSRI exposure during pregnancy and offspring ADHD after controlling for confounders.[12] Our study provides additional support for these results by showing that there is no association for ASD or ADHD when offspring exposed to SSRIs are directly compared to offspring whose mothers were in treatment for

FIGURE 2 Adjusted hazard ratios (HR) and 95% CIs for offspring diagnoses. Note: Adjusted HR and 95% CIs of offspring diagnoses when comparing offspring exposed prenatally to selective serotonin reuptake inhibitors (SSRIs) with offspring exposed to maternal psychiatric disorder but no medication (panel A), and with offspring born to mothers who discontinued SSRI use before pregnancy (panel B). ADS = autism spectrum disorder; ADHD = attention-deficit/hyperactivity disorder.
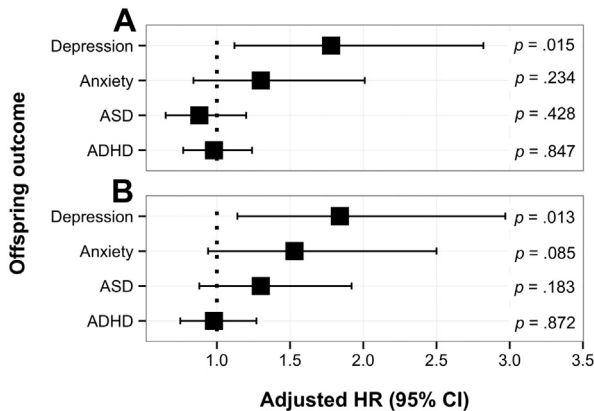
a depression-related disorder during pregnancy. However, our results are contrary to a study including nearly 300 children with ASD in the Kaiser Permanente health system,[13] and 2 other population-based studies,[14,28] both suggesting an association between SSRI use during pregnancy and ASD, the latter observing an association specifically with second- and third-trimester exposure in offspring of women predominantly of lower socioeconomic status.[28] Furthermore, a case-control study including 2,243 children with ADHD showed an association between antidepressant exposure during pregnancy and ADHD after controlling for maternal depression.[11] The discrepancy between that study and our negative finding might be explained by the fact that the prior study analyzed maternal depression regardless of whether it occurred before or during pregnancy, whereas we focused on maternal depression and related disorders close to and during pregnancy, that is, the time period with a particularly high risk for offspring adversity.

Taken together, our results related to offspring risk of ASD or ADHD after gestational exposure to SSRIs are reassuring. However, if SSRI exposure during gestation has delayed but significant effects on offspring risk for depression, research regarding timing of exposure and considerations regarding antidepressant mechanism of action and increased use of validated psychotherapies[29] may be needed to maximize maternal benefits while minimizing risk to the long-term health of the developing fetus. Clearly, further research is needed to follow offspring through adolescence; given the typical age of onset of depression, this would substantially increase the sample size as well as the generalizability of the findings. Meanwhile, until either confirmed or refuted, these findings must be balanced against the substantial adverse consequences of untreated maternal depression. &

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