The Association Between Antenatal Exposure to Selective Serotonin Reuptake Inhibitors and Autism:
A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: This systematic review and meta-analysis examines the relationship between antenatal selective serotonin reuptake inhibitor (SSRI) exposure and child autism, with specific attention to maternal mental illness (MMI) as a potential confounding factor.

Data Sources: We searched MEDLINE, Embase, PsycINFO, and CINAHL from database inception to January 28, 2016.

Study Selection: Keywords included terms for SSRIs, pregnancy, and autism. We included published, peer-reviewed articles written in English.

Data Extraction: Two reviewers used standardized instruments for data extraction and quality assessment. We generated pooled estimates for studies of the same design for SSRI exposure at any time during pregnancy and exposure during the first trimester. Subanalyses were conducted among studies with analyses (1) adjusted for MMI and (2) restricted to MMI.

Results: We included in the meta-analysis 4 case-control studies and 2 cohort studies. In the case-control studies, the adjusted pooled odds ratio (aPOR) values were 1.4 (95% CI, 1.0–2.0) (any) and 1.7 (95% CI, 1.1–2.6) (first trimester). In MMI-adjusted analyses, only first trimester exposure remained statistically significant (aPOR = 1.8; 95% CI, 1.1–3.1). In MMI-restricted analyses, neither exposure period was statistically significant. In the cohort studies, MMI-adjusted relative risk values were 1.5 (95% CI, 0.9–2.7) (any) and 1.4 (95% CI, 1.0–1.9) (first trimester). In MMI-restricted analyses, SSRI exposure at any time during pregnancy was nonsignificant.

Conclusions: It remains unclear whether the association between first trimester SSRI exposure and child autism that was present in the case-control studies even after adjustment for MMI is a true association or a product of residual confounding. Future studies require robust measurement of MMI prior to and during pregnancy.

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Autism is a neurodevelopmental disorder that is marked by impairments in social interaction and communication and by stereotyped patterns of behavior.[1] Both genetic and environmental factors are thought to play a role in the etiology of autism. Due to increasing autism rates (from 6.7 cases per 1,000 children in 2000 to 14.7 cases per 1,000 children in 2010),[2] there has been a recent focus on environmental determinants that could explain the higher prevalence.

The serotonin hypothesis of autism suggests that fetal exposure to high levels of serotonin could lead to the autism phenotype.[3] Selective serotonin reuptake inhibitors (SSRIs) are antidepressant medications that are used to treat depression and anxiety in approximately 6% of pregnant women in the United States.[4] These medications block serotonin reuptake in the presynaptic terminals, thereby increasing serotonin in the synaptic cleft. Selective serotonin reuptake inhibitors cross both the placental and fetal blood-brain barriers[5,6]; thus, there is concern about fetal exposure. It is thought that antenatal exposure to elevated serotonin levels results in dysfunctional serotonin signaling and that the resulting loss of serotonin terminals is associated with autism.[7] Every year, more than 500,000 pregnancies in the United States are complicated by depression or anxiety.[8] There is therefore an urgent need for accurate portrayal and interpretation of existing evidence regarding the association between antenatal SSRI exposure and autism so that appropriate treatment decision making can be supported.[9]

Several case-control and cohort studies[10–12] have examined the association between antenatal SSRI exposure and autism, with inconsistent results. There have also been several attempts at summarizing the literature on this topic, including a systematic review and meta-analysis[13] and a comprehensive review of the literature.[14] However, controversy surrounding interpretation of the association between antenatal SSRI exposure and autism remains. One major issue is that of the role of underlying maternal mental illness (eg, depression, anxiety, and other disorders that are indications for SSRI use). Maternal mental illness may have a direct negative impact on fetal and developmental outcomes[15] or may increase the risk for child autism because of shared genetic susceptibility between underlying mental illness and neurodevelopmental disorders.[16]

The purpose of this systematic review and meta-analysis was to describe, evaluate, and synthesize the evidence surrounding the risk of autism in the children of women exposed to selective serotonin reuptake inhibitors during pregnancy, with systematic consideration of the potential confounding role of underlying maternal mental illness.

Clinical Points

- Several case-control and cohort studies have examined the association between antenatal selective serotonin reuptake inhibitor (SSRI) exposure and child autism. There is much controversy surrounding this association, and the potential confounding role of maternal mental illness has not been thoroughly investigated.
- Our findings suggest to practitioners and to mothers who have taken or who are considering taking SSRIs during pregnancy that the reported associations between antenatal SSRI exposure and autism are likely to be confounded by maternal mental illness—although whether this and other confounders fully account for the increased risk remains unclear.

METHODS

Data Sources

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[17] Search terms for the systematic review of the literature were developed in collaboration with a research librarian. We used the following subject headings and keywords: (1) for SSRIs: *selective serotonin reuptake inhibitor**, *SSRI**, *serotonin uptake inhibitor**, *serotonin*, *fluoxetine*, *citalopram*, *paroxetine*, *sertraline*, *fluvoxamine*, *escitalopram*, *depressive disorder/drug therapy*, or *antidepressive agent**; (2) for pregnancy: *pregnant wom?n*, *pregnan**, or *pregnancy complications/drug therapy*; and (3) for autism: *autism spectrum disorder**, *ASD**, *autistic disorder*, *pervasive development disorder**, or *child developmental disorder**. The "explode" feature was used for subject headings to include all narrower derivatives. We searched the following databases from their inception until January 28, 2016: MEDLINE, Embase, PsycINFO, and CINAHL. One author (H.K.B.) conducted the initial database search. The bibliographies of all reviews and all original articles selected for full text review were hand searched to identify articles missed in the initial database search.

Study Selection

We included all published, peer-reviewed articles written in English that included women exposed to SSRIs during pregnancy and that reported original data. Studies that examined antidepressants in general as opposed to SSRIs specifically (ie, fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, and/or escitalopram) were excluded. We also excluded studies that examined autism-like symptoms (eg, poor social responsiveness) as opposed to a diagnosis of autism or autism spectrum disorder using validated clinical measures or diagnoses recorded in administrative databases. We included all eligible studies in the qualitative synthesis; if more than 1 article was published using the same data sources and overlapping study periods and samples, we selected the study that was deemed to have the highest quality (as per our systematic quality assessment as described below) for the quantitative synthesis.

Data Extraction

Two authors (H.K.B. and N.H.-S.) independently extracted data from the selected articles using a standardized data extraction form, which was created a priori. The form included the following components based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[18]: study design and setting, data sources, sample size and inclusion and exclusion criteria, exposure measurement (ie, antidepressants examined and exposure windows), outcome measurement, and control for confounders. We extracted unadjusted and adjusted odds ratios (ORs) or relative risks (RRs) and their 95% confidence intervals (CIs) to calculate pooled effect estimates. Discrepancies in the data extracted by the 2 authors were resolved through discussion.

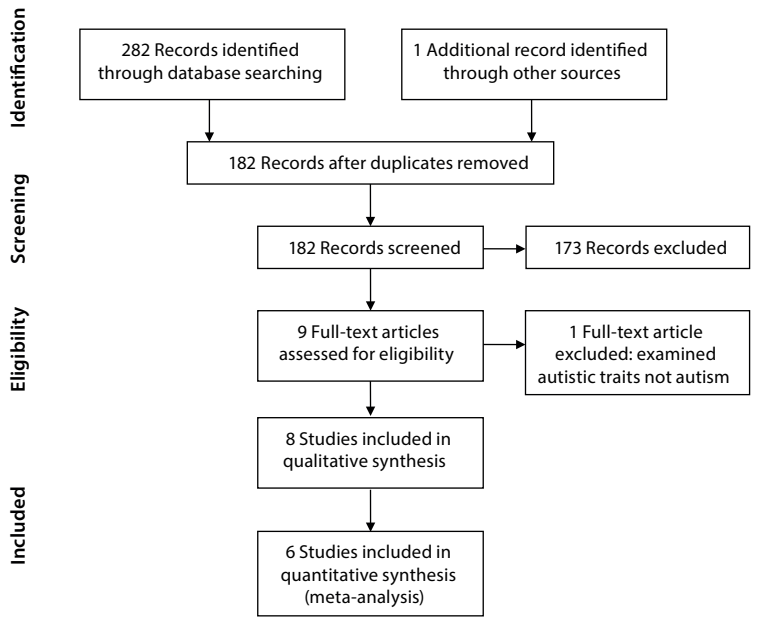
Quality Assessment

Two authors (H.K.B. and N.H.-S.) independently conducted a quality assessment for each article. Study quality was assessed using a previously published quality assessment tool, the Systematic Assessment of Quality in Observational Research (SAQOR).[19] The SAQOR was developed to assess the quality of the literature regarding the risks and benefits of antidepressant medication use during pregnancy and is an expansion of the Downs and Black[20] and Newcastle-Ottawa[21] scales, which do not explicitly consider the role of confounding by indication. The SAQOR assesses the quality of 19 criteria falling into the following categories: sample, control group, exposure/outcome measurement, follow-up (for prospective cohort studies), confounding, and reporting of data. Therefore, using SAQOR, we could systematically evaluate control for maternal mental illness (ie, confounding by indication). We also identified other confounders a priori that, based on existing literature, may be associated with both SSRI exposure and child autism risk: other psychotropic medication use during pregnancy; maternal age; parity; maternal income, education, or occupation; smoking during pregnancy; and child sex.[22] Based on these 19 criteria, SAQOR produces a final quality rating: high, moderate, low, or very low. This rating is then modified based on study design according to the Grading of Recommendations Assessment, Development, and Evaluation system[23]; randomized controlled trials are upgraded and cross-sectional studies are downgraded. Case-control studies and cohort studies use the "unmodified" SAQOR ratings: high (5/5 criteria = adequate), moderate (4/5 criteria = adequate), low (3/5 criteria = adequate), and very low (2/5 criteria = adequate). On the basis of previous studies[19,24] using the SAQOR criteria, we planned to exclude studies of very low quality from the meta-analysis. Discrepancies in quality assessment ratings assigned by the 2 authors were discussed until consensus was reached.

Data Synthesis

We used DerSimonian and Laird[25] random effects models to estimate the pooled ORs or RRs and 95% CI for the association between antenatal SSRI exposure and autism.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram



We calculated unadjusted and adjusted pooled ORs and RRs for any SSRI exposure during pregnancy and for first trimester SSRI exposure, which is hypothesized to be the most etiologically relevant exposure window.[3] To specifically address the potential confounding effect of maternal mental illness, we considered that confounding by indication can be addressed through the analytic plan (ie, through stratification and adjustment for confounders) as well as through the design of a study (ie, through sample restriction and matching). Therefore, we additionally generated (1) adjusted pooled ORs and RRs including only studies that adjusted for current or past maternal mental illness such as depression, anxiety, or other psychiatric diagnoses; and (2) pooled ORs and RRs from samples where both exposed and unexposed pregnancies occurred in women with a history of mental illness (restricted analyses). By holding known maternal mental illness status constant across SSRI and non-SSRI groups, these methods allowed us to better examine autism risk unconfounded by maternal mental illness. Because only 2 studies were included in this latter analysis, we used a fixed-effects model.

We conducted sensitivity analyses to test the impact of model assumptions and biases on our results. First, we examined the source of variance between studies by calculating the Q and I^2 statistics.[26] A nonsignificant Q statistic and a small I^2 value (<25%) suggest that observed variation is due to random variation and not real heterogeneity across studies. Second, we reestimated the pooled ORs and RRs using a fixed-effects model, which assumes that the true effect is the same for all studies and assigns more extreme weights to studies than the random-effects models.[26] Finally, we reestimated the pooled ORs and RRs, excluding studies 1 by 1 to determine the influence of a given study. Statistical analyses used the Comprehensive Meta-Analysis software (Biostat Inc, Englewood, New Jersey).

RESULTS

Search Results

Figure 1 shows the article selection process. Database searches revealed 181 articles. Hand searches of the bibliographies of all systematic reviews and meta-analyses and all articles selected for full text review revealed 1 additional article missed in the initial search. On the basis of title and abstract, 173 studies were excluded and 9 full-text articles were retrieved and reviewed in detail. One study[27] was excluded because it examined autism-like symptoms rather than autism diagnosis. Three studies (1 case-control study and 2 retrospective cohort studies)[12,28,29] from Denmark used the same data sources and had overlapping study periods and samples. All 8 eligible studies were included in the qualitative synthesis and quality assessment. However, to ensure inclusion of only unique studies in the quantitative synthesis, we excluded 2 of the Danish studies[28,29] and retained the study that had the highest quality primary analysis as per our systematic quality assessment.[12] Therefore, the meta-analysis included 6 unique studies: 4 case-control studies[10,11,30,31] and 2 retrospective cohort studies.[12,32]

Characteristics of Included Studies

Characteristics of the 8 studies included in the qualitative synthesis are presented in Table 1. One study[32] was conducted in Canada, 3 in the United States,[10,11,30] 3 in Denmark,[12,28,29] and 1 in Sweden.[31] All studies had similar samples; most exclusion criteria related to study feasibility issues (eg, subjects with missing data or maternal/child pairs that could not be linked). Hviid et al[12] excluded children with congenital anomalies that could be related to autism, implying the presence of a genetic syndrome as the autism etiology; Boukhris et al[32] excluded children born preterm. Seven studies used administrative data of some kind: hospital records,[10] insurance records,[11] or provincial/national registers.[12,28,29,31,32] In a case-control study, Harrington et al[30] used primary data collection, with recruitment of cases through developmental service providers. Six studies[10–12,28,29,32] used administrative prescription data to measure SSRI exposure during pregnancy. Rai et al[31] and Harrington et al[30] used maternal self-report during pregnancy or after delivery, respectively. All of the studies except 1 determined autism status by using diagnostic codes recorded in administrative data. Harrington et al[30] used validated diagnostic interviews (ie, the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule).

Table 1. Characteristics of Studies Examining Antenatal Exposure to Selective Serotonin Reuptake Inhibitors (SSRIs)

Study	Location, Dates Born and Diagnosed	Data Sources	Sample Size	Exclusion Criteria	Exposure Definition	Outcome Definition	Confounders Controlled for
Case-control studies							
Clements et al, 2015[10]	US Born: not stated Diagnosed: 1997–2010	Partners HealthCare electronic health records (hospital data)	Cases: 1,377 Controls: 4,022	Children not linked to mothers; intellectual disability (for controls only?); 1 child per mother	Specific selective serotonin reuptake inhibitors (SSRIs) unclear Dispensing date or days supplied overlapped with period before delivery, preconception, 1st trimester, 2nd trimester, 3rd trimester	Any medical claim: *ICD-9* code for pervasive developmental disorder (299) including autism	Maternal age, ethnicity, median income, insurance type; child sex, birth year; maternal depression Matched on child sex, birth year, birth facility, ethnicity, insurance type, preterm vs full-term birth
Croen et al, 2011[11]	US Born: 1995–1999 Diagnosed: 1995–2002	Childhood Autism Perinatal Study (Kaiser Permanente insurance data)	Cases: 298 Controls: 1,507	Mothers without full drug benefits; 1 child per mother	Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline Dispensing date or days supplied overlapped with period before delivery, preconception, 1st trimester, 2nd trimester, 3rd trimester	Any medical claim: *ICD-9* codes for autism (299.0), Asperger syndrome (299.8), pervasive developmental disorder (299.9)	Maternal age, ethnicity, education; child sex, birth weight, birth year, birth facility; maternal mental illness Matched on child sex, birth year, birth facility
Gidaya et al, 2014[28]	Denmark Born: 1997–2005 Diagnosed: 1999–2011	Danish registries (administrative data)	Cases: 5,212 Controls: 52,150	Children not linked to mothers; gestational age < 23 or > 43 weeks	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline Dispensing date or days supplied overlapped with period before delivery, preconception, 1st trimester, 2nd trimester, 3rd trimester	Any medical claim by a psychiatrist: *ICD-10* codes for childhood autism (F84.0), atypical autism (F84.1), Asperger syndrome (F84.5), pervasive developmental disorder (F84.8, F84.9)	Parental age, socioeconomic status; child sex; parental mental illness Matched on birth month and year
Harrington et al, 2014[30]	US Born: 1998–2007 Diagnosed: not stated	Childhood Autism Risks from Genetics and Environment (CHARGE) Study (service data [cases], birth files [controls])	Cases: 492 Controls: 320	Non-English or Spanish mothers; children not living with biological mother, < 2 or > 5 years old	Citalopram, escitalopram, fluoxetine, paroxetine, sertraline Maternal postdelivery self-report of exposure by month: before delivery, 1st trimester, 2nd trimester, 3rd trimester (validated against charts)	Autism spectrum disorder as measured by Autism Diagnostic Interview-Revised and Autism Diagnostic Observation Schedule	Maternal birth place; child birth year, birth facility Matched on child sex, child age, treatment facility
Rai et al, 2013[31]	Sweden Born: 1995–? Diagnosed: before 2007	Stockholm youth cohort within Swedish registries (administrative data)	Cases: 1,679 Controls: 16,845	Mothers with missing identification numbers; children adopted, in Stockholm < 4 y	Citalopram, fluoxetine, paroxetine, sertraline Maternal self-report of exposure at first antenatal interview only: before delivery (validated against charts)	Any medical claim plus specialist claim: *ICD-9* code for pervasive developmental disorder (299) including autism; *ICD-10* code for pervasive developmental disorder (F84), including autism; *DSM-IV* code for pervasive developmental disorder (299) including autism	Parental age, maternal parity, income, education, occupation; maternal birth country; maternal mental illness Matched on child sex, birth month and year

(continued)

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Table 1 (continued). Characteristics of Studies Examining Antenatal Exposure to Selective Serotonin Reuptake Inhibitors (SSRIs)

Study	Location, Dates Born and Diagnosed	Data Sources	Sample Size	Exclusion Criteria	Exposure Definition	Outcome Definition	Confounders Controlled for
Cohort studies							
Boukhris et al, 2015[32]	Canada Born: 1998–2009 Diagnosed: before 2009	Quebec registries (administrative data)	Exposed: 1,583 Unexposed: 142,924	Mothers without full drug benefits; gestational age <37 wk, multiple births	Citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline Dispensing date overlapped with 2nd or 3rd trimester	Any medical claim: *ICD-9* codes for autism (299.0), Asperger's syndrome (299.8), pervasive developmental disorder (299.9); *ICD-10* codes for childhood autism (F84.0), atypical autism (F84.1), Asperger syndrome (F84.5), pervasive developmental disorder (F84.8, F84.9)	Maternal age, education, social assistance, residence, chronic medical conditions; child sex, birth year; maternal mental illness; pre-pregnancy or 1st trimester SSRI use
Hviid et al, 2013[12]	Denmark Born: 1996–2005 Diagnosed: before 2010	Danish registries (administrative data)	Exposed: 6,068 Unexposed: 620,807	Multiple births, no information on gestational age, genetic conditions associated with autism	Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline Dispensing date overlapped with period before delivery, preconception, 1st trimester	Any medical claim by a psychiatrist: *ICD-10* codes for childhood autism (F84.0), atypical autism (F84.1), Asperger syndrome (F84.5), pervasive developmental disorder (F84.8, F84.9)	Maternal age, parity, country of origin, birth place, residence, education, employment, smoking; maternal mental illness; other maternal drug use
Sørensen et al, 2013[29]	Denmark Born: 1996–2006 Diagnosed: before 2010	Danish registries (administrative data)	Exposed: 7,506 Unexposed: 646,782	Mothers with missing information; gestational age <23 or >43 wk, adopted, died in first year	Specific SSRIs unclear Dispensing date overlapped with period before delivery, 1st trimester, 2nd or 3rd trimester	Any medical claim by a psychiatrist: *ICD-10* codes for childhood autism (F84.0), atypical autism (F84.1), Asperger syndrome (F84.5), pervasive developmental disorder (F84.8, F84.9)	Parental age, parity; child sex, birth weight, gestational age; parental mental illness (except affective disorders)

Quality of Included Studies

Details of the SAQOR quality assessment are included in Table 2. All of the studies met the criteria for an adequate sample. Three of the study samples may not have been representative of the broader population; Croen et al[11] and Boukhris et al[32] conducted their studies in low socioeconomic samples and Harrington et al[30] selected cases from among children receiving developmental services. All but 1 of the case-control studies were marked by small numbers of antenatal SSRI exposures. The number of exposed cases in these studies ranged from 14 to 33 subjects for any SSRI exposure during pregnancy and from 14 to 23 subjects for first trimester SSRI exposure. All studies met the criteria for an adequate control or comparison group, but several studies did not meet the criteria for adequate measurement of exposure and outcome. Rai et al[31] relied on SSRI exposure self-reported at the first antenatal interview, and Harrington et al[30] relied on SSRI exposure self-reported retrospectively when children were on average 3.7 years of age (this approach being particularly prone to recall bias). Three studies[12,29,32] considered pregnancies to be exposed to SSRIs if there was a onetime SSRI dispensation that occurred during the exposure windows of interest. In contrast, 3 stronger studies[10,11,28] examined the overlap of both dispensing date and days of medication supplied with the exposure windows using administrative data gathered throughout pregnancy. Boukhris et al[32] included only second and third trimester SSRI exposure in their definition of any SSRI exposure.

None of the case-control studies met the criteria for adequate consideration of distorting influences. Harrington et al[30] did not control for maternal mental illness at all; Clements et al[10] controlled only for maternal depression (and not other indications for SSRI use). The retrospective cohort study by Hviid et al[12] had the best consideration of distorting influences according to our a priori criteria; this study controlled for maternal age, parity, country of origin, birthplace, residence, education, employment, smoking during pregnancy, maternal mental illness, and other drug use. The other 2 retrospective cohort studies by Boukhris et al[32] and Sørensen et al[29] failed to control for some key confounders (eg, maternal depression, other psychotropic medication use).

Three studies[10,11,29] overadjusted for variables potentially on the causal pathway between antenatal SSRI exposure and autism (eg, gestational age, birth weight). Beyond the main multivariable models, several studies included sensitivity analyses to try to isolate the effects of SSRI exposure, for example, by restricting analyses to women with mental illness,[11,12,30] examining the association between

Table 2. Assessment of Study Quality According to Systematic Assessment of Quality in Observational Research (SAQOR)[a]

	Case-Control Studies					Cohort Studies		
Criterion	Clements et al, 2015[10]	Croen et al, 2011[11]	Gidaya et al, 2014[28]	Harrington et al, 2014[30]	Rai et al, 2013[31]	Boukhris et al, 2015[32]	Hviid et al, 2013[12]	Sørensen et al, 2013[29]
Sample								
Sample is representative	✓		✓		✓		✓	✓
Source is clear	✓	✓	✓	✓	✓	✓	✓	✓
Sampling method is clear	✓	✓	✓	✓	✓	✓	✓	✓
Sample size is appropriate			✓			✓	✓	✓
Entry criteria are clear and justified	✓	✓	✓	✓	✓		✓	✓
Overall rating (3/5 = adequate)	✓	✓	✓	✓	✓	✓	✓	✓
Control/comparison group								
Control group is included	✓	✓	✓	✓	✓	✓	✓	✓
Control group is easily identifiable	✓	✓	✓	✓	✓	✓	✓	✓
Source of control group is appropriate		✓	✓		✓	✓	✓	✓
Controls are matched or randomized	✓	✓	✓	✓	✓	✓	✓	✓
Statistical differences are controlled for								
Overall rating (3/5 = adequate)	✓	✓	✓	✓	✓	✓	✓	✓
Quality of exposure/outcome measures								
Measure of exposure is adequate		✓	✓					
Measure of outcome is adequate	✓	✓	✓	✓	✓		✓	✓
Overall rating (2/2 = adequate)		✓	✓					
Distorting influences								
Mental illness is controlled for	✓[b]	✓	✓		✓	✓	✓	✓[c]
Other psychotropic drugs are controlled for							✓	
All other confounders are controlled for								
Overall rating (2/3 = adequate)							✓	
Reporting of data								
Missing data are explained	✓	✓	✓	✓	✓	✓	✓	✓
Data are clearly and adequately presented	✓	✓	✓	✓	✓	✓	✓	✓
Overall rating (2/2 = adequate)	✓	✓	✓	✓	✓	✓	✓	✓
Final quality rating[d,e]	L	M	M	L	L	L	M	L

[a]Check (✓) denotes that the criterion was rated as adequate.
[b]Controlled only for maternal depression and not other psychiatric diagnoses, which may be indications for SSRI treatment.
[c]Controlled for mental illnesses other than affective disorders.
[d]Follow-up criteria are not included because none of the studies under examination were prospective.
[e]Final quality rating: H = high (5/5 criteria = adequate), M = moderate (4/5 criteria = adequate), L = low (3/5 criteria = adequate), and VL = very low (2/5 criteria = adequate).

paternal mental illness or use of SSRIs and child autism,[29,31] and comparing outcomes among siblings with and without exposure to SSRIs.[29] A detailed description of these analyses is included in Supplementary eTable 1.

It is important to note that all included studies that maternal mental illness relied on psychiatric diagnoses recorded in administrative databases. Therefore, measurement could have been affected by underidentification of maternal mental illness.[10–12] Moreover, definitions of maternal mental illness varied across studies. All studies met the criteria for adequate reporting of data. Overall, the studies were rated as moderate quality[11,12,28] or low quality.[10,29–32]

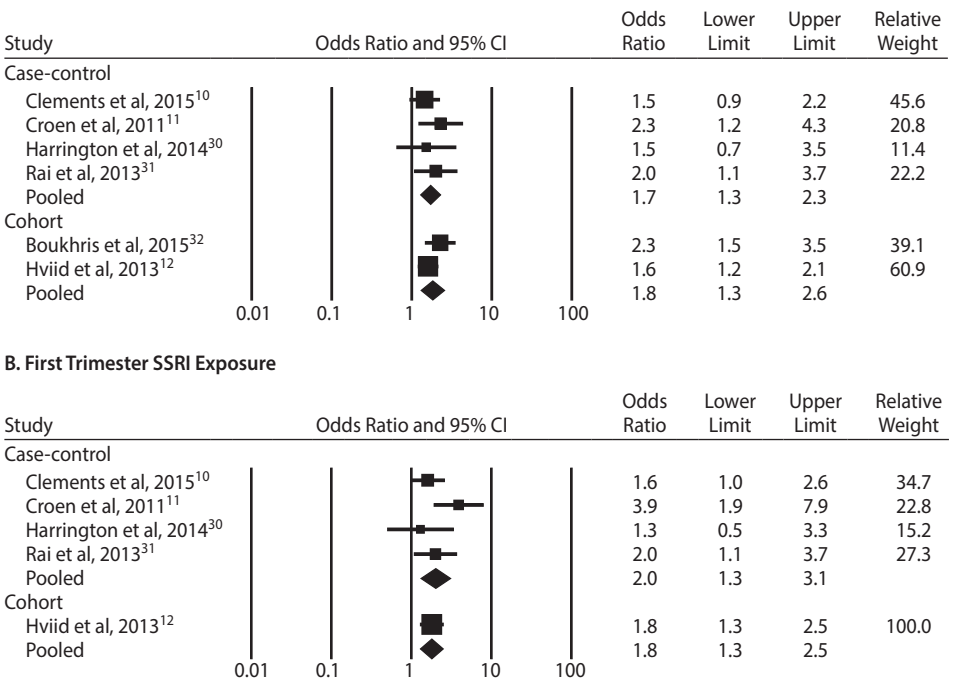
Meta-Analysis

On the basis of the quality assessment of the studies' main analyses, all studies met the minimum level of quality necessary for the meta-analysis. Of the 3 studies[12,28,29] using the same data sources and overlapping study periods and samples, we retained the study with the highest quality.[12] Because 2 of these studies, the case-control study by Gidaya et al[28] and the retrospective cohort study by Hviid et al,[12] had the same final quality rating, we retained the retrospective cohort study, which had better control for distorting influences.[12] Therefore, in the main analyses, there were 4 case-control studies (3,864 cases and 22,694 controls) and 2 retrospective cohort studies (7,651 exposed and 763,731 unexposed).

Figure 2 shows the unadjusted associations between any SSRI exposure during pregnancy (panel A) and first trimester SSRI exposure (panel B) and autism. For the 4 case-control studies, the unadjusted pooled OR for any SSRI exposure was 1.7 (95% CI, 1.3–2.3); for first trimester SSRI exposure, it was 2.0 (95% CI, 1.3–3.1). For the retrospective cohort studies, the unadjusted pooled RR for any SSRI exposure was 1.8 (95% CI, 1.3–2.6). The unadjusted RR for the 1 retrospective cohort study that reported first trimester SSRI exposure was 1.8 (95% CI, 1.3–2.5).

Figure 3 shows the adjusted associations for the studies that provided adjusted estimates for any SSRI exposure during pregnancy (panel A) and for first trimester SSRI exposure (panel B). For the 4 case-control studies, the pooled adjusted OR for any SSRI exposure was 1.4 (95% CI, 1.0–2.0; $P = .04$); for first trimester SSRI exposure, it was 1.7 (95% CI, 1.1–2.6). Figure 3 also shows the adjusted associations for the studies that accounted for

Figure 2. Unadjusted Associations Between Antenatal Selective Serotonin Reuptake Inhibitor (SSRI) Exposure and Autism (all studies)



maternal mental illness as a confounding factor for any SSRI exposure during pregnancy (panel C) and for first trimester SSRI exposure (panel D). For the 3 case-control studies, the pooled adjusted OR for any SSRI exposure was 1.4 (95% CI, 0.9–2.2); for first trimester SSRI exposure, it was 1.8 (95% CI, 1.1–3.1). For the retrospective cohort studies, which both controlled for maternal mental illness, the pooled adjusted RR for any SSRI exposure was 1.5 (95% CI, 0.9–2.7). The adjusted RR for the 1 retrospective cohort study that reported first trimester SSRI exposure was 1.4 (95% CI, 1.0–1.9; $P = .07$).

In analyses restricted to women with a history of mental illness, the pooled estimate for the 2 case-control studies[11,30] that reported unadjusted ORs for any SSRI exposure during pregnancy was 1.5 (95% CI, 0.8–3.0). One of these case-control studies[30] also reported adjusted associations for any SSRI exposure during pregnancy and for first trimester SSRI exposure among women with a history of mental illness; their adjusted ORs were 1.9 (95% CI, 0.8–4.6) and 1.7 (95% CI, 0.7–4.4), respectively. One of the retrospective cohort studies[12] also reported on any SSRI exposure during pregnancy among a sample restricted to women with mental illness, with an adjusted RR of 0.6 (95% CI, 0.2–1.3).

Sensitivity Analyses

For all analyses, the Q statistic was nonsignificant and the I^2 value was relatively small, suggesting that the variation between the studies was due to random variation. Results were therefore unchanged when we used fixed-effects models instead of random-effects models for the main analyses.

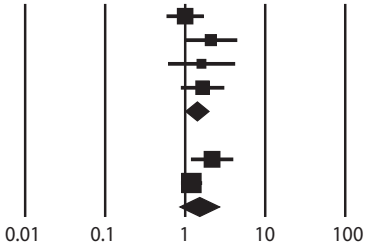
The studies by Clements et al[10] and Rai et al[31] accounted for most of the relative weight in the pooled analyses. When we reestimated the pooled ORs, excluding studies 1 by 1, removal of the study by Clements et al[10] did not affect results. However, when the study by Rai et al[31] was removed, the adjusted association for first trimester SSRI exposure became nonsignificant (adjusted pooled OR = 1.8; 95% CI, 1.0–3.5; $P = .07$). Although the study by Croen et al[11] had a small relative weight, its OR was consistently of the greatest magnitude. When this study was removed, the adjusted association for first trimester SSRI exposure became nonsignificant (adjusted pooled OR = 1.4; 95% CI, 1.0–2.1; $P = .06$).

DISCUSSION

Our systematic search of the literature revealed 5 case-control studies[10,11,28,30,31] and 3 retrospective cohort studies[12,29,32] examining the association between antenatal SSRI exposure and autism risk. The included studies were limited by recall bias and by poor control for distorting influences, particularly maternal mental illness. However, several studies reported sensitivity analyses aimed at isolating the effects of SSRI exposure, for example, by restricting samples to women with mental illness, by examining the impact of paternal mental illness, or by comparing siblings with and without antenatal SSRI exposure. Overall, the studies were rated as being of low to moderate quality. We pooled the results of 6 unique studies. Pooling the 4 case-control studies, we showed that associations between

Figure 3. Adjusted Associations Between Antenatal Selective Serotonin Reuptake Inhibitor (SSRI) Exposure and Autism (all studies and studies that controlled for maternal mental illness)

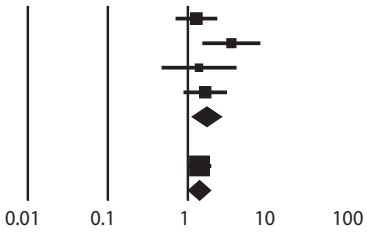
A. Any SSRI Exposure During Pregnancy, Adjusted (all studies)



Study	Odds Ratio and 95% CI	Odds Ratio	Lower Limit	Upper Limit	Relative Weight
Case-control					
Clements et al, 2015[10]		1.0	0.6	1.7	38.9
Croen et al, 2011[11]		2.1	1.0	4.4	19.8
Harrington et al, 2014[30]		1.6	0.6	4.1	12.2
Rai et al, 2013[31]		1.7	0.9	3.0	29.1
Pooled		1.4	1.0	2.0	
Cohort					
Boukhris et al, 2015[32]		2.2	1.2	3.9	40.0
Hviid et al, 2013[12]		1.2	0.9	1.6	60.0
Pooled		1.5	0.9	2.7	

0.01 0.1 1 10 100

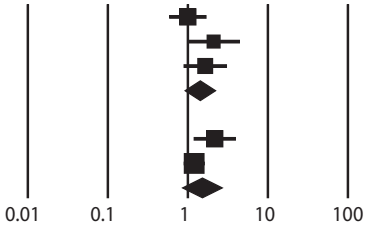
B. First Trimester SSRI Exposure, Adjusted (all studies)



Study	Odds Ratio and 95% CI	Odds Ratio	Lower Limit	Upper Limit	Relative Weight
Case-control					
Clements et al, 2014[10]		1.3	0.7	2.3	33.7
Croen et al, 2011[11]		3.5	1.5	7.9	20.8
Harrington et al, 2014[30]		1.4	0.5	4.0	13.5
Rai et al, 2013[31]		1.7	0.9	3.0	32.0
Pooled		1.7	1.1	2.6	
Cohort					
Hviid et al, 2013[12]		1.4	1.0	1.9	100.0
Pooled		1.4	1.0	1.9	

0.01 0.1 1 10 100

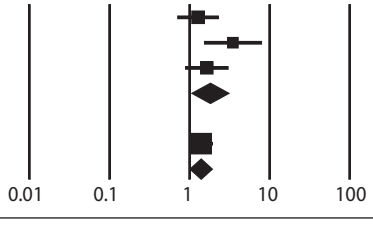
C. Any SSRI Exposure During Pregnancy, Adjusted (studies that controlled for maternal mental illness)



Study	Odds Ratio and 95% CI	Odds Ratio	Lower Limit	Upper Limit	Relative Weight
Case-control					
Clements et al, 2014[10]		1.0	0.6	1.7	40.7
Croen et al, 2011[11]		2.1	1.0	4.4	25.6
Rai et al, 2013[31]		1.7	0.9	3.0	33.7
Pooled		1.4	0.9	2.2	
Cohort					
Boukhris et al, 2015[32]		2.2	1.2	3.9	40.0
Hviid et al, 2014[12]		1.2	0.9	1.6	60.0
Pooled		1.5	0.9	2.7	

0.01 0.1 1 10 100

D. First Trimester SSRI Exposure, Adjusted (studies that controlled for maternal mental illness)



Study	Odds Ratio and 95% CI	Odds Ratio	Lower Limit	Upper Limit	Relative Weight
Cohort					
Clements et al, 2015[10]		1.3	0.7	2.3	37.6
Croen et al, 2011[11]		3.5	1.5	7.9	26.2
Rai et al, 2013[31]		1.7	0.9	3.0	36.2
Pooled		1.8	1.1	3.1	
Cohort					
Hviid et al, 2013[12]		1.4	1.0	1.9	100.0
Pooled		1.4	1.0	1.9	

0.01 0.1 1 10 100

antenatal SSRI exposure and autism were statistically significant, with slight attenuation of the effect estimate with adjustment. Among studies that specifically adjusted for maternal mental illness, the only effect that remained statistically significant was first trimester exposure. Pooled estimates from studies that reported on samples restricted to women with mental illness were all nonsignificant, but point estimates were similar to those of the analyses adjusting for maternal mental illness. In contrast, pooling 2 retrospective cohort studies that controlled for maternal mental illness, we showed that associations adjusted for maternal mental illness were nonsignificant. The estimate from the retrospective cohort study restricted to women with mental illness was also nonsignificant.

The major strength of this study is the systematic consideration of the potential confounding role of underlying maternal mental illness. By conducting subanalyses on studies that (1) adjusted for maternal mental illness and (2)

performed analyses in samples restricted to women with mental illness, we were able to assess the impact of maternal mental illness on the observed association between antenatal SSRI exposure and autism. Additional strengths are that we minimized reviewer selection bias by using an article selection strategy that was developed a priori in consultation with a research librarian and that 2 reviewers independently extracted the data and conducted the quality assessment. For the quality assessment, we used a tool, SAQOR, that was developed specifically to assess the quality of the literature regarding the risks and benefits of antidepressant medication use during pregnancy.[19] This tool is a significant improvement on the Downs and Black[20] and Newcastle-Ottawa[21] scales, which do not thoroughly consider the role of confounding.

Our ability to provide definitive conclusions about the relationship between antenatal SSRI exposure and autism was limited, however, by the quality and size of the included studies. Despite efforts to restrict our analyses to studies that met a minimum level of quality, included studies were most notably limited by information bias and by inadequate control for distorting influences identified a priori by our study team. For example, 2 of the case-control studies[30,31] relied on maternal self-report of antenatal SSRI exposure, thus potentially introducing recall bias. Most studies were also limited in their ability to fully account for maternal mental illness. Studies differed in the conditions included in their definitions of mental illness; for example, 1 study[10] controlled only for maternal depression while others controlled for a broader range of diagnoses. Therefore, even adjusted estimates may have been affected by residual confounding. The small number of studies was clearly a limiting factor. In sensitivity analyses, the exclusion of just 1 study had the potential to render pooled associations nonsignificant. The small numbers of exposures in the case-control studies may have limited our ability to detect statistically significant effects in certain subanalyses (ie, the subanalyses restricted to women with mental illness in particular could have been underpowered to detect an effect). Because most confidence intervals, whether statistically significant or not, were close to the null value, results should be interpreted with caution. We were also unable to examine publication bias since there was an insufficient number of studies from which to create a valid funnel plot.[33] One could argue that pooled estimates should have been omitted from our article due to these underlying issues; however, a summary statistic based on existing literature, though limited, will provide a valuable reference point to which future, better-designed studies can compare their results.

Considering our findings in the context of recent literature, a previous meta-analysis[13] found a statistically significant pooled association between any antenatal antidepressant exposure and autism when 4 case-control studies were combined (adjusted pooled OR = 1.8; 95% CI, 1.5–2.4).[11,15,30,31] The magnitude of the pooled OR in our study was lower (for the 4 case-control studies, adjusted pooled OR = 1.4; 95% CI, 1.0–2.0). This difference may be explained by our inclusion of a recently published case-control study[10] that had nonsignificant results and the exclusion of a study[27] that examined autism symptoms but not diagnosis. When we further excluded a study[30] that did not adjust for maternal mental illness, the effect became nonsignificant for any SSRI exposure (adjusted pooled OR = 1.4, 95% CI, 0.9–2.2). To our knowledge, no other meta-analysis has conducted subanalyses focused on first trimester exposure only or analyzed the potential impact of maternal mental illness on the association between antenatal SSRI exposure and autism as we did.

The findings of this study—namely, the attenuated observed risk after adjusting for and restricting to maternal mental illness—support the hypothesis that maternal mental illness is a confounding factor in the association between antenatal SSRI use and child autism risk. One possible mechanism is that of a shared genetic predisposition for mental illness and autism.[34–37] For example, genome-wide single nucleotide polymorphism (SNP) data show that specific SNPs are associated with autism, bipolar disorder, and schizophrenia.[34] Moreover, family history studies[37,38] of children with autism consistently show a large number of family members with mental illness. Second, exposure to maternal mental illness during pregnancy may directly negatively affect fetal and child neurodevelopment through the impact on the fetal hypothalamic-pituitary-adrenal axis.[15,39] The association between maternal stress and autism-like behaviors has been shown in both animal[40] and human studies.[41]

However, maternal mental illness and other factors did not completely explain the increased risk for autism after first trimester exposure to SSRIs in the pooled case-control studies (although in the retrospective cohort study, the relationship was completely attenuated). The question that remains, therefore, is whether the association between first trimester SSRI exposure and autism that was present in the case-control studies even after adjustment for maternal mental illness is a true association or a product of residual confounding. The association between first trimester exposure to SSRIs and autism is plausible, as supported by several lines of evidence. First, serotonin plays an important role in prenatal and postnatal brain development.[42–44] It is involved in cell division, cell differentiation, and synaptogenesis[42–44] and regulates the development of dopamine and other neurotransmitters.[43] Second, 30% of children with autism have elevated platelet serotonin levels.[45,46] This association has been consistently shown in diverse populations,[45] and the phenomenon is unique to autism and is not observed in children who have only developmental delay.[46] Third, animal studies have shown an association between prenatally altered serotonin levels (ie, exposure to serotonin agonists or medications that increase serotonin) and autism-like behaviors in adulthood.[47] However, it is also possible that this finding can be explained by inadequate control for confounding factors since no case-control studies adjusted for all a priori–defined confounders and there were limitations to the measurement of maternal

mental illness, even in the studies where it was considered. For example, in some studies, not all maternal psychiatric diagnoses were captured.[10] Further, some studies measured maternal illness only during pregnancy. If the association between antenatal SSRI exposure and autism is due to shared genetic risk, controlling for maternal mental illness during pregnancy alone will not completely control for confounding; maternal pre-pregnancy mental illness will also be important.[48] A further fact supporting a role for residual confounding in the first trimester pooled estimates is the nonsignificant adjusted estimate in the retrospective cohort study,[12] which had the largest number of SSRI exposures and the most robust control for confounding of all the studies in this review (see Table 2).

Much controversy has surrounded the association between antenatal SSRI exposure and autism. Our analyses showed statistically significant associations between first trimester SSRI exposure and autism in pooled case-control studies, even after adjustment for maternal mental illness, although the association was not present in a well-designed retrospective cohort study. Our findings suggest to practitioners and to mothers who have taken or who are considering taking SSRIs during pregnancy that reported associations between antenatal SSRI exposure and autism are likely to be confounded by maternal mental illness—although whether this and other confounders fully account for the increased risk remains unclear. We are reassured by the null findings of the well-designed retrospective cohort study,[12] but the fact that the exclusion of even 1 study had the potential to change the statistical significance of the analysis should make us cautious in our interpretation and supports the need for additional high-quality research before more definitive conclusions can be made about the role of antenatal SSRI exposure in the etiology of autism. These studies should account for the underlying confounding effect of maternal mental illness by using complete and robust measurement of depression, anxiety, and other psychiatric diagnoses that may also be associated with autism risk both prior to and during pregnancy. In the meantime, clinicians and patients must continue to consider the risks of relapse and untreated maternal mental illness in decisions about the use of SSRI medication in pregnancy.

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Drug names: citalopram (Celexa and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others).

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: The Association Between Antenatal Exposure to Selective Serotonin Reuptake Inhibitors and Autism: A Systematic Review and Meta-Analysis

Authors: Hilary K. Brown, PhD; Neesha Hussain-Shamsy, MHS; Yona Lunsky, PhD; Cindy-Lee E. Dennis, PhD; and Simone N. Vigod, MD

DOI Number: 10.4088/JCP.15r10194

List of Supplementary Material for the article

1. eTable 1 Sensitivity analyses to determine the causal role of selective serotonin reuptake inhibitors

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table 1. Sensitivity analyses to determine the causal role of selective serotonin reuptake inhibitors

Study	Sensitivity analysis approach	Any SSRI exposure
Case-control studies		
Croen et al., 2011[11]	Antenatal SSRI exposure and autism in children of mothers with *any mental illness*	OR 1.6 (95% CI 0.6-4.0)
Gidaya et al., 2014[28]	Antenatal SSRI exposure and autism in children of mothers with *any mental illness*	"Effect estimates were close to the null"
	Antenatal SSRI exposure and autism in children of mothers with *depression*	"Effect estimates were close to the null"
Harrington et al., 2014[30]	Antenatal SSRI exposure and autism in children of mothers with *any mental illness*	aOR 1.9 (95% CI 0.8-4.6)
		1st trimester: aOR 1.7 (95% CI 0.7-4.3)
Cohort studies		
Hviid et al., 2013[12]	Antenatal SSRI exposure and autism in children of mothers with *depression*	aRR 0.6 (95% CI: 0.2-1.3)
Sorensen et al., 2013[29]	Antenatal SSRI exposure and autism in children of mothers with *depression and bipolar disorder*	aRR 1.4 (95% CI 0.8-2.4)
	Paternal SSRI exposure and autism in children	aRR 1.1 (95% CI 0.7-1.6)
	Antenatal SSRI exposure and autism in exposed and unexposed siblings	aRR 0.9 (95% CI 0.4-2.0)

The following studies did not conduct sensitivity analyses specifically for SSRIs (although some conducted sensitivity analyses for antidepressants broadly): Clements et al., 2014[10]; Rai et al., 2013[31]; Boukhris et al., 2015[32]