

Title:

Exposure to Selective Serotonin Reuptake Inhibitors during Pregnancy and Risk of Autism Spectrum Disorder in Children: A Systematic Review and Meta-analysis of Observational Studies

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Abstract:

This study is a critical analysis of the association between selective serotonin reuptake inhibitors (SSRIs) exposure during pregnancy and autism spectrum disorder (ASD) risk in children. Electronic databases were searched for observational studies published from January 1946 to June 2014 related to the association between SSRI exposure during pregnancy and ASD in children. Studies relevant to the association between SSRI exposure during pregnancy and ASD in children were extracted and compiled for meta-analysis evaluation. Ninety-five citations were identified and seven observational studies were included. Four case-control studies were eligible for the meta-analysis and two cohort studies were narratively reviewed. The pooled crude and adjusted odds ratios of the case-control studies were 2.13 (95% CI 1.66-2.73) and 1.81 (95% CI 1.47-2.24) respectively. Low heterogeneity was observed between studies. The two population-based cohort studies; utilized the same Denmark data set, have conflicting results. The findings of this meta-analysis and narrative review support an increased risk of ASD in children of mothers exposed to SSRIs during pregnancy; however, the causality remains to be confirmed.

Keywords: SSRI, serotonin reuptake inhibitor, autism spectrum disorder, pregnancy

Main Text:

Introduction

Untreated maternal depression has been associated with poor health outcomes for both mothers and children (Sontag-Padilla et al. 2013). Antidepressants are therefore indicated for pregnant women if the benefits outweigh the risk (National Institute for Health and Clinical Excellence 2007; Joint Formulary Committee 2014). Selective serotonin reuptake inhibitors (SSRIs) are the most frequently prescribed anti-depressant classes. Substantial placental transfer occurs with SSRIs (Rampono et al. 2009) and may cause unwanted effects to the unborn child. Currently, meta-analysis results demonstrate that SSRI exposure during pregnancy is associated with preterm birth and low birth rate (Huang et al. 2014), congenital malformation (Myles et al. 2013), and persistent pulmonary hypertension (Grigoriadis et al. 2014). The use of SSRIs in pregnant women is a complex decision that requires weighing the effectiveness of treating depressive symptoms while considering potential adverse events in mother and child.

Recent studies have indicated a possible association between the use of SSRIs in pregnancy and the risk of autism spectrum disorder (ASD) in children (Croen et al. 2011; Eriksson et al. 2012; Gidaya et al. 2014; Harrington et al. 2014; Hviid et al. 2013; Rai et al. 2013; Sorensen et al. 2013). SSRIs are able to cross not only the blood-brain barrier for intended pharmacological actions but also the placental barrier for possible unintended consequences (Kendall-Tackett and Hale 2010). This is evidenced by the high SSRI cord/maternal distribution ratio, i.e., 0.70-0.86 (Rampono et al., 2009). Animal studies demonstrate that transient usage of fluoxetine during early development produces abnormal emotional behaviors in adult mice, suggesting the role of serotonin transporter modulation during development of brain systems involved in emotional and stress related responses (Ansorge et al. 2004). Pharmacokinetic and pharmacodynamic data, albeit weak and indirect in nature, suggest a plausible biological mechanism between in-utero exposure of SSRIs and ASD in children. However, in the scientific literature, evidence of this association contradicted several epidemiological studies supporting a positive association (Croen et al. 2011; Eriksson et al. 2012; Gidaya et al. 2014; Sorensen et al. 2013) whilst others indicated no association (Harrington et al. 2014; Hviid et al. 2013; Rai et al. 2013). Given conflicting results from studies, it is difficult to reach a consensus as to whether there is a link between the use of SSRIs in pregnancy and ASD in children.

ASD affects 1 in 88 children in the United States (US) and prevalence is approximately 1 to 1.2% in the United Kingdom (UK) (Baird et al. 2006; Baron-Cohen et al. 2009). Due to ASD's early onset, their lifelong persistence and associated pervasive impairment (Simonoff et al. 2008), there is significant impact on social outcomes, education and health of patients and their families (Bolton et al. 1998; Buescher et al. 2014). In the US and UK, the cost of supporting an ASD individual with intellectual disability throughout their lifetime is estimated to be US\$2.2-2.4 million and US\$1.4 million for an ASD individual without intellectual disability (Buescher et al. 2014). Additionally, there is a high prevalence of mental health conditions in individuals with ASD, including attention deficit hyperactivity disorder, global and specific learning disabilities, emotional disorders, anxiety and depressive disorders, and chronic tic disorder (Bradley and Bolton 2006; Green et al. 2005; Simonoff et al. 2008). Understanding the risk factors for the development of ASD is an important public health issue.

In view of the above issues, we undertook a systematic review and meta-analysis of published observational studies to evaluate whether SSRI exposure during pregnancy increases the risk of ASD in children.

Method

A systematic literature search was conducted using the search terms (SSRI OR Serotonin uptake inhibitor OR antidepressant) AND pregnancy AND (autism OR autistic OR pervasive developmental disorder OR Asperger syndrome OR Asperger's syndrome OR ASD). PubMed, EMBASE, PsycINFO and the Cochrane Review databases were searched up to 25 June 2014. English titles and abstracts were screened and full texts of relevant articles were retrieved for further review to identify relevant studies. A hand-search of selected articles was conducted to further identify pertinent studies. This study was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) for the flow chart and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) to ensure clear and comprehensive reporting.

Inclusion and exclusion criteria

Observational studies, including cohort and case-control study designs, which investigated the association between SSRI use and ASD were included. Case reports and animal studies were excluded.

Quality assessment

As recommended by the Cochrane Collaboration (Higgins and Green 2011), the methodological quality of the included studies were assessed using the Newcastle-Ottawa Scale (NOS) (Wells et al. 2000). Two authors (HT and LW) independently reviewed and scored each study. Separate NOS criteria were used for case control and cohort studies. A maximum of nine stars could be allocated for the following categories: selection, comparability and outcome/exposure. The total score was obtained by adding the number of stars in the sub-categories where a higher score indicated better quality.

Data extraction

Data from the included studies were extracted using a standardized data collection form. These included study duration and design, data source, covariates, exposure groups, and sample size. Authors HT and LW independently extracted data and completed the characteristics form that was subsequently cross-matched to ensure consistency and accuracy.

Outcome parameters such as relative risk (RR), crude odds ratio (OR), adjusted OR and the corresponding 95% confidence intervals (CI) were extracted and included in the meta-analysis if appropriate.

The primary outcome of interest was the risk or odds of developing ASD following exposure to SSRIs, either at preconception, or during pregnancy.

Statistical analysis

To estimate the association between the use of SSRIs during pregnancy and ASD in children, the results of the included studies were combined using DerSimonian and Laird's random-effects model (DerSimonian and Laird 1986) to account for heterogeneity among studies. The Mantel-Haenszel fixed-effect model was used to validate the results and control for overweighting of the

included small studies. All formulations of SSRIs were included. Analysis was performed on both the crude and adjusted estimates from the studies. The pooled estimates with 95% CI were calculated.

Sensitivity analysis was performed to assess the robustness of the results. This was conducted by substituting the findings of Rai et al. (2013) with those of Eriksson et al. (2012) as the subjects in these two studies came from the same data source.

As the studies included in the analysis were carried out in different settings, we examined the extent of heterogeneity among studies with the Cochran Q test (Higgins and Green 2011), where a cut-off p -value of 0.1 was considered significant for heterogeneity. Higgin's I^2 -statistic (Higgins and Green 2011) was reported for each figure.

The background incidence rate of ASD was calculated by dividing the total number of ASD cases by the total number of people at risk in the respective data source. The corresponding 95% confidence intervals were obtained using the Poisson method.

All probability values (two tailed) with a p -value of 0.05 were considered statistically significant. All analyses were conducted using Review Manager 5.2 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) and SAS version 9.3 (SAS Institute Inc., Cary, NC, United States).

Results

PubMed, EMBASE, PsycINFO and the Cochrane Review databases were searched; yielding 26, 53, 16 and 0 records respectively, with a total of 95 articles, from 1 January 1946 to 25 June 2014. Seventy-one records remained after the removal of duplicates. Titles and abstracts were screened and full texts of relevant articles were retrieved for further review with 64 studies meeting the exclusion criteria. Seven observational studies (Croen et al. 2011; Eriksson et al. 2012; Gidaya et al. 2014; Harrington et al. 2014; Hviid et al. 2013; Rai et al. 2013; Sorensen et al. 2013) were found to be relevant to the research question (Figure 1). All the studies used healthcare databases in their analyses. Disease codes such as the International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and ICD-10) were used to identify cases, except for the study of Harrington et al., which used the Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS)

(Table 1). Included studies were of adequate quality with respect to study design, obtaining more than seven out of nine stars from the NOS quality assessment (Table 2).

Four case-control studies (Croen et al. 2011; Gidaya et al. 2014; Harrington et al. 2014; Rai et al. 2013) were eligible for the main meta-analysis, representing a total of 79,221 patients and controls. Rai et al. (2013) and Eriksson et al. (2012) used the same database; therefore Eriksson et al. was substituted for Rai et al. in a sensitivity analysis. Two cohort studies (Hviid et al. 2013; Sorensen et al. 2013) that used the same data source were narratively reviewed separately.

Meta-analysis

Four case-control studies (Croen et al. 2011; Gidaya et al. 2014; Harrington et al. 2014; Rai et al. 2013) were meta-analyzed. Two were from US (Croen et al. 2011; Harrington et al. 2014) and the others were from Denmark (Gidaya et al. 2014) and Sweden (Rai et al. 2013) (Table 1). The commencing years of the studies ranged from 1995 (Croen et al. 2011) to 2010 (Harrington et al. 2014). In all case-control studies, children without an ASD diagnosis were the controls and samples were randomly taken from the corresponding databases (Croen et al. 2011; Gidaya et al. 2014; Harrington et al. 2014; Rai et al. 2013; Eriksson et al. 2012). The use of SSRIs during pregnancy was significantly associated with an increased risk of ASD in children (pooled crude OR=2.13; 95% CI 1.66 to 2.73). No heterogeneity was found between studies (Q -statistics=0.5, p =0.92; I^2 =0%) and thus, there was no difference between the random and fixed-effects model (Figure 2). The results remained similar and significant using the adjusted OR from each study (pooled adjusted OR=1.81; 95% CI 1.47 to 2.24) (Figure 3).

Sensitivity analysis by replacing Rai et al. (2013) with Eriksson et al. (2012) showed similar results (pooled crude OR=2.37; 95% CI 1.83 to 3.05) (Figure 4). However, low heterogeneity was observed (Q -statistics=3.97, p =0.26; I^2 =24%) and a slightly different estimate was found from the random-effects model (pooled crude OR=2.42; 95% CI 1.74 to 3.37) (Figure 5).

Narrative review

Two cohort studies were included in this review. Both studies were conducted in Denmark using the Danish Civil Registration System, Danish National Prescription Registry and Danish Psychiatric Central Register as data sources (Hviid et al. 2013; Sorensen et al. 2013). Hviid et al.

conducted a cohort study of all live singletons in Denmark from 1996 to 2005, with follow-up to 2009 (626,875 births). Through linkage between maternal use of SSRIs and children diagnosed with ASD on the Danish database, a survival analysis of time to diagnosis in the children was used to estimate the incidence of ASD according to the use of SSRIs in mothers during pregnancy. Hviid et al. identified 3,892 ASD cases in their cohort with a background incidence rate of 77 per 100,000 person-years. Compared with no SSRI exposure, however, the risk of ASD with exposure was not significantly increased (adjusted rate ratio=1.20; 95% CI 0.90 to 1.61).

Likewise, Sorensen et al. (2013) identified 655,615 children born in their cohort from 1996 to 2006. Using a similar linkage method, they captured 5,437 children with a diagnosis of ASD, which was slightly higher than the rate in Hviid et al. (2013) (0.21% higher; 95% CI 0.18% to 0.24%). In contrast, Sorensen et al. (2013) found a significant association between the use of SSRIs during pregnancy and the risk of ASD in children (adjusted hazard ratio=1.6; 95% CI 1.3 to 2.0).

The background incidence rate of ASD was obtained from four studies (Gidaya et al. 2014; Hviid et al. 2013; Rai et al. 2013; Sorensen et al. 2013). The rate ranged from 5.91 to 8.48 per 1,000 patients. Significant differences between the incidence rates were observed (Figure 6). As three out of four incidence rates were from the same data source, a pooled estimate was not compiled.

Discussion

To our knowledge, this is the first systematic review and meta-analysis of SSRI use in pregnancy and risk of ASD in children. Based on the results from the meta-analyses of the case control studies and review of cohort studies, **SSRI exposure during pregnancy appears to be associated with the risk of ASD in children.**

Three out of four published case-control studies reported significantly positive association between SSRI exposure during pregnancy and ASD in children (Croen et al. 2011; Gidaya et al. 2014; Rai et al. 2013). Although Harrington et al. (2014) reported non-significant results for the total sample, a statistically significant result was demonstrated when only males were considered. Additionally, since the sample size in Harrington et al. (2014) was the smallest of the studies (n=812), the statistically non-significant finding may be due to insufficient statistical power.

The pooled results in our meta-analysis of the four case-control studies (Croen et al. 2011; Gidaya et al. 2014; Harrington et al. 2014; Rai et al. 2013) gives an adjusted odds ratio of 1.81 (95% CI

1.47-2.24) with low heterogeneity among the studies ($I^2 = 0.00$). The identified studies were conducted in several countries (United States, Sweden and Denmark) using different data sources. However, they yielded similar results for risk (adjusted OR between 1.55 and 2.2). This lends further support to an association between SSRI exposure during pregnancy and ASD in children.

The two population-based cohort studies which utilized the same Danish dataset had slightly different results (Hviid et al. 2013; Sorensen et al. 2013). Sorensen et al. (2013) reports significant results (adjusted HR=1.6; 95% CI 1.3-2.0), while Hviid et al. (2013) demonstrated non-significant results in the fully adjusted model (adjusted IRR=1.20; 95% CI 0.90-1.61). There were differences between the two cohort studies with respect to the number of cases (3,892 in Hviid et al. and 5,437 in Sorensen et al.) and the incidence rate of ASD (5.9 per 1,000 patients in Hviid et al. and 8.3 per 1,000 patients in Sorensen et al.). Both studies share similar inclusion criteria but there were differences in the exclusion criteria. One key difference was that Hviid et al. excluded children with genetic conditions (Table 1), which may potentially confound the study results, while Sorensen et al. did not. By excluding high risk children, it is expected that the number of ASD cases and the incidence rate will be lower in Hviid et al., potentially reducing the statistical power to detect an increased risk of less than 20% in the SSRI treatment group. Alternatively, it is possible that Sorensen et al.'s results are confounded by the inclusion of genetic conditions in children. However, it is also worth noting that secondary analysis in Hviid et al.'s study showed a statistically significant association between SSRI usage 2 years to 6 months before pregnancy and ASD in children (adjusted IRR=1.46; 95% CI 1.17-1.81).

Although the results indicate an increased risk of ASD in children exposed to SSRIs during pregnancy, we cannot exclude any potential confounding effect on ASD detection in the studies. Pregnant women with SSRI exposure are likely to have a greater frequency of medical consultations during and after pregnancy compared to non-exposed women (Sontag-Padilla et al. 2013). In turn, their children may have more frequent medical encounters compared to other children, which could lead to a higher rate of ASD detection. As a result, we cannot exclude the possibility that the positive association is due to better detection of ASD in these children. If an increased risk were solely due to better detection, we would also expect an increased risk of ASD in children of mothers on other antidepressants during pregnancy. Both Croen et al. (2011) and Sorensen et al. (2013) provided evidence that this is not the case. Neither identified a significant association between the use of other

antidepressants (tricyclics, dual-action antidepressants and serotonin-norepinephrine reuptake inhibitors) during pregnancy and the risk of ASD in children (Croen et al. 2011; Sorensen et al. 2013). Both studies used medical databases as their data source with a reasonable sample size (1,805 in Croen et al and 648,097 in Sorensen et al). Their results do not support the idea that the risk of ASD in children will be higher due to greater detection.

The incidence rate of ASD in four studies were also estimated (Gidaya et al. 2014; Hviid et al. 2013; Rai et al. 2013; Sorensen et al. 2013) and Hviid et al. was found to have a lower rate (5.91 in 1,000 patients) despite the same data source as in studies by Sorensen et al. (2013) and Gidaya et al. (2014). Variation in Hviid et al.'s (2013) exclusion criteria which excluded children with a number of genetic conditions, may have contributed to the difference in ASD incidence rate (Table 1).

Studies investigating the association between SSRI in pregnancy and the risk of ASD in children in the literature are scant, possibly due to difficulties conducting studies in this area. As interventional studies would not be ethical in this clinical setting, observational studies appear to be more appropriate for investigating this association. However, obtaining a large sample size from a non-database study is challenging, with long follow-up time in the cohort setting and recall bias in the case-control setting being major methodological limitations to carrying out and drawing unbiased conclusions from such studies. Data linkage between mother and child is not possible or available in many databases currently used internationally adding to significant limitations in addressing this important association.

Strengths and Limitations

We undertook a rigorous systematic review and meta-analysis including all relevant literature to date. Reviewer selection bias was minimized by using a predefined search strategy for selection and data extraction was conducted by two independent authors.

Differences in study designs, exclusion criteria, control groups and duration of follow-up can affect the accuracy of pooled estimates for both crude and adjusted ORs. However, the findings from different case-control studies were consistent with the pooled estimates, which support our findings of an increased risk of ASD in children exposed to SSRIs during pregnancy.

As the number of studies included in the meta-analysis is limited, a funnel plot was not performed as it would not reliably identify publication bias. In addition, the studies identified for meta-

analysis are relatively recent (2011-2014) with similar results; therefore we cannot exclude the possibility of publication bias. As a result, the pooled estimates may be overestimated.

Conclusion

The findings of this meta-analysis and narrative review of epidemiological studies support an increased risk of ASD in children exposed to SSRIs during pregnancy; however, causality remains to be confirmed. In view of the challenges and difficulties in evaluating this association, further replication studies in this area are recommended.

Conflicts of interests:

Prof. Wong and Prof. Simonoff receive grant from Innovative Medicines Initiative (IMI) for the European Autism Interventions (EU-AIMS) project. Prof. Simonoff also receives funding from National Institute for Health Research Programme Grant for Applied Research: Improving outcomes for people with autism spectrum disorder by reducing mental health problems) and from Autism Speaks (Why do people with autism fare so differently in adult life?) and well as the NIHR Biomedical Research Centre for Mental Health; No other relationships or activities have been declared that could appear to have influenced the submitted work.

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Table 1. Characteristics of the included studies

Study	Data Source	Study period	Country	Inclusion criteria	Exclusion criteria	Control definition	Exposure duration definition
Croen 2011	Kaiser Permanente Medical Care Program in Northern California (KPNC)	1995-2002	United States	Born in KPNC facility between January 1995 and June 1999; remained in health plan for at least 2 years following birth; at least 1 diagnosis of autism (ICD-9-CM code 299.0), Asperger syndrome (ICD-9-CM code 299.8), pervasive developmental disorder not otherwise specified (ICD-9-CM code 299.8)	Restricted to 1 child per mother; restricted to children whose mothers were KPNC members with full pharmacy benefits in the year before delivery; excluded 16 controls whose medical records contained an ASD diagnosis recorded after initial control selection	Children without an ASD diagnosis were randomly sampled from the remaining cohort at a ratio of 5 controls per case matched by sex, birth year and hospital of birth	Any SSRI prescription for mothers in the year prior to delivery
Eriksson 2012	Autism Centre for Young Children in Stockholm; Swedish medical birth register; Statistical Central Bureau of Sweden	2002-2008	Sweden	Registered with a clinical diagnosis of ASD between 2005 and 2008 in the county, drawn from a population-based group of children; born between 2002 and 2006	Families unable to speak Swedish or English; children moved abroad; children referred to general rehabilitation centers due to complex needs in addition to ASD; families declined invitation	Children born alive in Stockholm County during the period 2002–2006 without a clinical diagnosis of ASD	Any antidepressant use during pregnancy
Hviid 2013	Danish Medical Birth Registry; Danish National Prescription Registry; Danish Psychiatric Central Register; Danish Civil Registration	1996-2010	Denmark	Live births in Denmark during the study period of January 1, 1996, through December 31, 2005; with known gestational age and singleton births	Children with genetic conditions (fragile X syndrome, tuberous sclerosis, Angelman’s syndrome, Down’s syndrome, DiGeorge’s syndrome, neurofibromatosis, and Prader–Willi syndrome) and congenital	Women without SSRI prescriptions from 2 years before pregnancy through delivery	Any SSRI use during the period from 4 weeks before the beginning of the pregnancy until delivery

	System				rubella syndrome		
Rai 2013	Stockholm Youth Cohort; Swedish National and Regional Register; Stockholm County Adult Psychiatric Outpatient Register; Swedish medical birth register	2001-2007	Sweden	All children 0-17 years old, residing in Stockholm County between 2001 and 2007 with ASD defined by codes from the international classification of diseases, ninth and tenth revisions, ICD-9 (299) and ICD-10 (F84), respectively, or <i>Diagnostic and Statistical Manual of Mental Disorders</i> , fourth edition, (299)	Missing maternal identification numbers; adopted children; living in Stockholm County less than 4 years	Children in Stockholm Youth Cohort without ASD diagnosis matched by sex, birth month and birth year in a ratio of 1 case to 10 controls	Any SSRI use reported by mothers at their first antenatal interview
Sorensen 2013	Danish Medical Birth Registry; Danish National Prescription Registry; Danish Psychiatric Central Register; Danish Civil Registration System; Danish National Hospital Register	1996-2010	Denmark	Antidepressant drugs with ATC code N06A with exposure window from 30 days before conception to the day of birth; time of conception after 1 February 1996	Children with missing or extreme values of gestational age (≤ 23 weeks and ≥ 45 weeks) were excluded; missing information about mothers; adopted children; children who died during the first year of life	Women without SSRI prescriptions from 30 days before conception to the day of birth	Any SSRI usage from 30 days before conception to the day of birth.
Gidaya 2014	Danish Drug Prescription Register; Danish Psychiatric Central Register; Danish Civil Registration System; Danish National Hospital Register	1997-2011	Denmark	Children born in Denmark between January 1, 1997 and December 31, 2006; All biological singletons and one child randomly selected from multiple births; subjects' records from 1 January 1999 to 31 March 2011 were searched for International Classification	Children not linked to biological mother; mother not living in Denmark a year before delivery; child's gestational age <23 weeks or >43 weeks	Children from the Danish Civil Registration System without ASD admission diagnoses. Ten controls per case were individually matched on birth	Any SSRI exposure from 3 months prior to the estimated date of conception to birth

				of Diseases codes (ICD-10) of: F840, F841, F845, F848, and F849		month and year	
Harrington 2014	CHARGE Standardized telephone interview	2003-2010	United States	Children with ASD or other development disorders aged 2-5 years old and born in California; had at least one parent who speaks English or Spanish; living with at least one biological parent and in catchment area of specified California Regional Centers that coordinate services for those with developmental disabilities	Siblings of probands were excluded, regardless of case status	Identified using state birth files; matched to autism cases by age, sex and regional center (targeted 4:1 male to female ratio)	Any SSRI use 3 months before conception to the end of pregnancy.

Table 2: Quality assessment of the included studies by the Newcastle-Ottawa Scale

Study	Design	Selection	Comparability	Exposure/Outcome	Total
Croen 2011	Case-control	****	**	***	9
Eriksson 2012	Case-control	****	**	**	8
Hviid 2013	Cohort	****	**	***	9
Rai 2013	Case-control	****	**	***	9
Sorensen 2013	Cohort	****	**	***	9
Gidaya 2014	Case-control	****	**	***	9
Harrington 2014	Case-control	****	**	*	7

Table 3. Summary of results of the included studies

Study	Number of participants	Number of events	Crude OR^a/RR^b/HR^c	Factors considered during adjusted analysis	Adjusted OR/RR/HR
Croen 2011	1805	ASD group: 15 with exposure; 283 without exposure Control group: 34 with exposure; 1473 without exposure	2.3 (95% CI ^d 1.2-4.3)	Age; race/ethnicity; level of maternal education; birth weight; sex; child's year of birth and birth facility	2.2 (95% CI 1.2-4.3)
Eriksson 2012	173578	ASD group: 8 with exposure; 180 without exposure Control group: 1714 with exposure; 171676 without exposure	4.45 (95% CI 2.19-9.05)	Not available	Not available
Hviid 2013	626875	SSRIs group: 52 with ASD; 6016 without ASD Control group: 3752 with ASD; 617055 without ASD	1.62 (95% CI 1.23-2.13)	Age; calendar period; mother's age at birth; country of origin; place of residence; parity; psychiatric diagnoses before delivery; other drug use during pregnancy; smoking status; employment status; level of education	1.20 (95% CI 0.90-1.61)
Rai 2013	47706	ASD group: 14 with exposure; 4415 without exposure Control group: 71 with exposure; 43206 without exposure	2.03 (95% CI 1.13-3.66)	Maternal age; any maternal psychiatric disorder; paternal age; parental income; education; occupation; maternal country of birth; birth parity	1.65 (95% CI 0.90-3.03)
Sorensen 2013	654288	SSRIs group: 91 with ASD; 7415 without ASD Control group: 5333 with ASD; 641449 without ASD	1.9 (95% CI 1.5-2.4)	Maternal age at conception; paternal age at conception; parental psychiatric history (except maternal affective disorder); gestational age; birth weight; sex; parity	1.6 (95% CI 1.3-2.0)
Gidaya 2014	57365	ASD group: 76 with exposure; 5139 without exposure Control group: 365 with exposure; 51785 without exposure	2.2 (95% CI 1.6-2.7)	Parental age; sex of the child; history of maternal depression; other SSRI indications; child's birth, month and year	1.8 (95% CI 1.4-2.3)

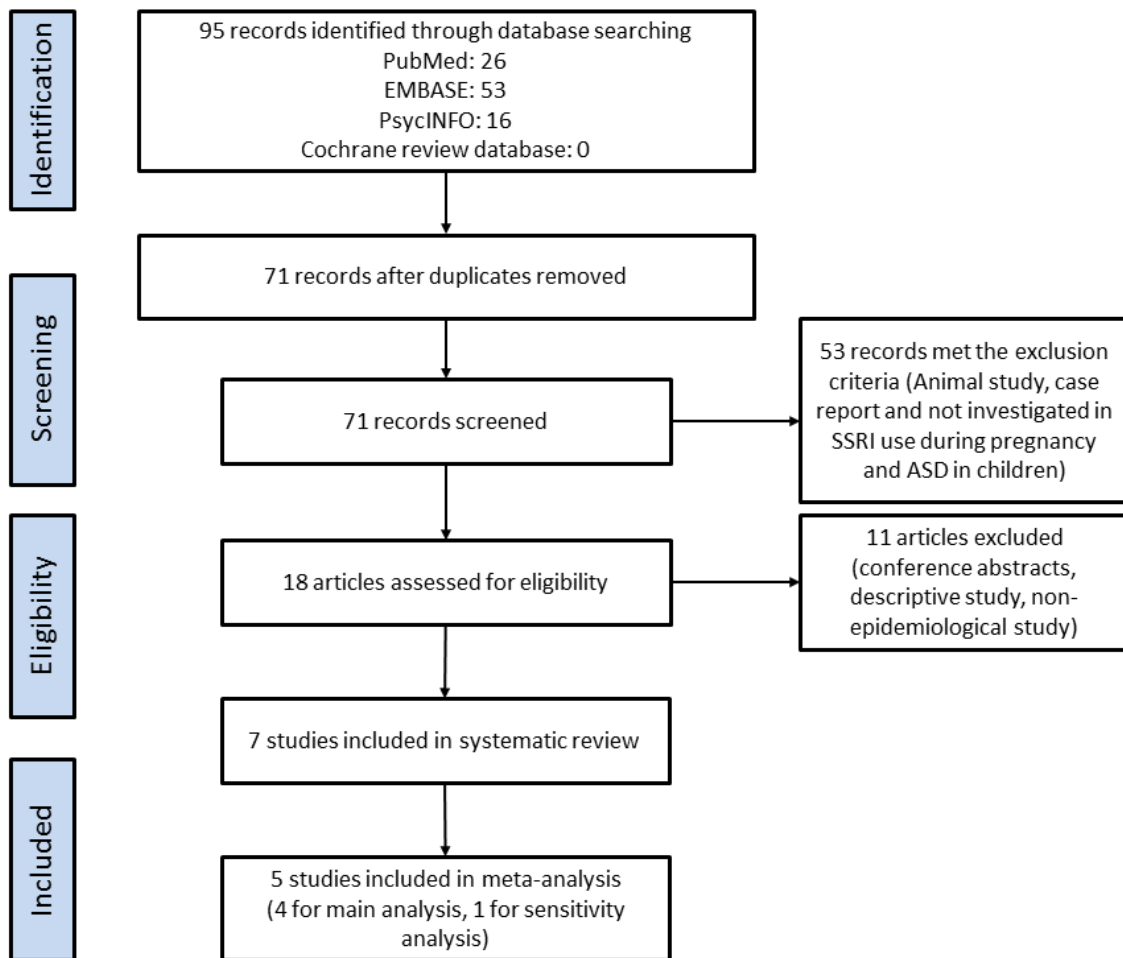
Harrington 2014	812	ASD group: 29 with exposure; 463 without exposure Control group: 11 with exposure; 309 without exposure	1.52 (95% CI 0.65-3.53)	Regional center; child's year of birth; mother's birthplace	1.55 (95% CI 0.59-4.08)
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^aOR=Odds Ratio

^bRR=Rate Ratio,

^cHR=Hazard Ratio

^d95% CI=95% confidence interval



Abbreviations: SSRI=Selective Serotonin Reuptake Inhibitors ; ASD=Autism Spectrum Disorder.

Figure 1: PRISMA Flowchart

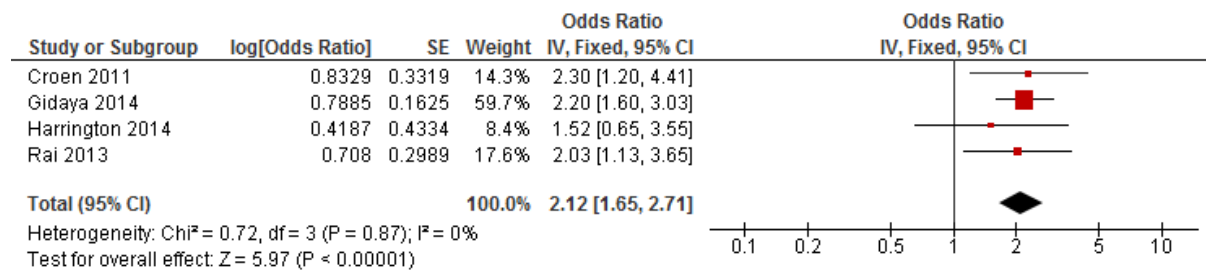


Figure 2: Meta-analysis of Crude Odds Ratios

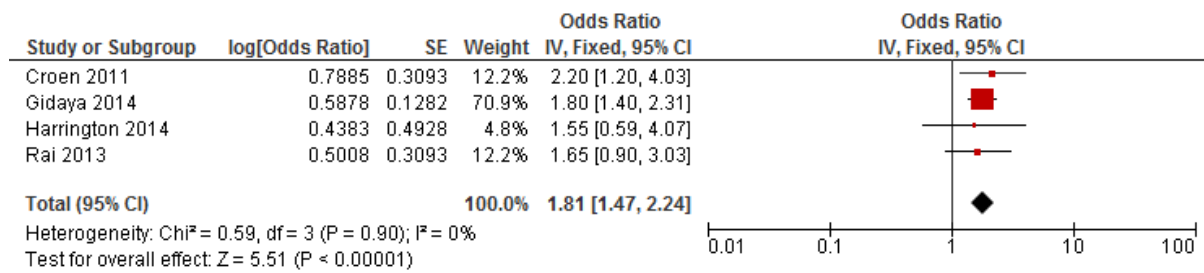


Figure 3: Meta-analysis of the Adjusted Odds Ratios

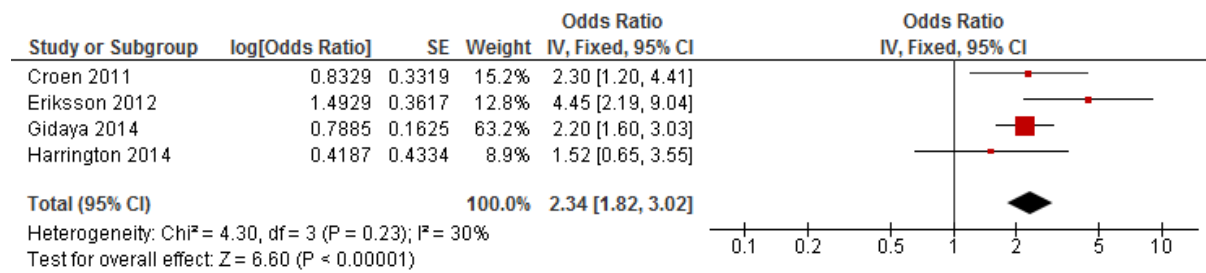


Figure 4: Sensitivity Analysis: Meta-analysis of Crude Odds Ratios (fixed effect model)

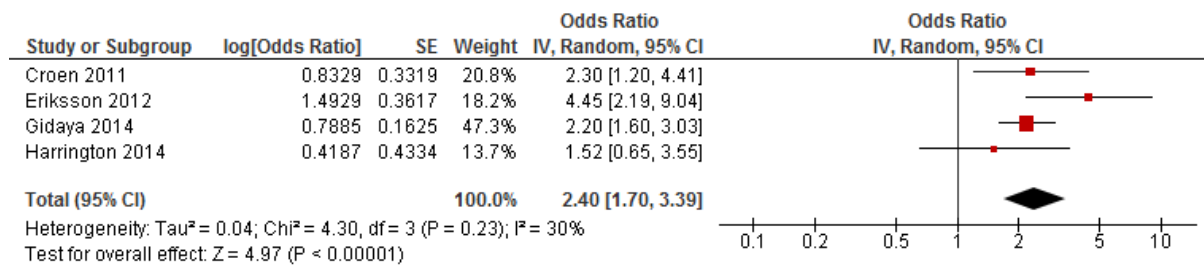
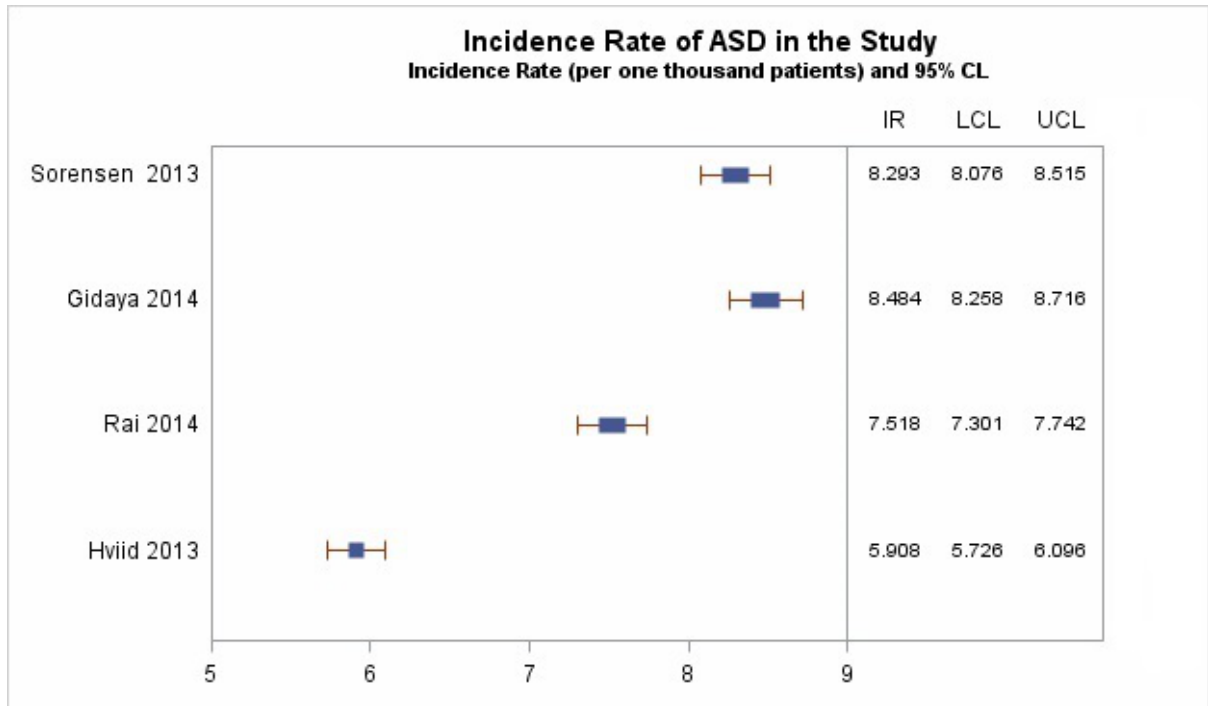


Figure 5: Sensitivity Analysis: Meta-analysis of Crude Odds Ratios (random effect model)



IR=Incidence rate per one thousand patients
 LCL=95% lower confidence limit
 UCL=95% upper confidence limit

Sorensen 2013, Gidaya 2014 and Hviid 2013 used the same Danish database; therefore meta-analysis was not performed.

Figure 6: Summary Plot of Incidence Rate of ASD