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METHODS IN CLINICAL PHARMACOLOGY

Maternal SSRI discontinuation, use, psychiatric disorder and the risk of autism in children: a meta-analysis of cohort studies

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We undertook an exclusive meta-analysis of cohort studies investigating the possible link between prenatal selective serotonin reuptake inhibitor (SSRI) exposure and autism spectrum disorders (ASD) in children to further investigate our previous suggestion of confounding by indication. The point estimates regarding the following cohorts were extracted and pooled: (1) pregnant women who discontinued SSRI until 3 months before pregnancy; (2) pregnant women who were exposed to SSRI during pregnancy; and (3) pregnant women with maternal psychiatric disorder but no exposure to SSRI during pregnancy. Although the pooled point estimate of the first cohort showed a trend for increase, it did not reach significance. The pooled point estimates of the latter cohorts showed a significant association with ASD which strengthens our previous suggestion of confounding by indication. Future studies should be adequately designed to differentiate whether the previously suggested association is a result of maternal psychiatric disorder or SSRI exposure or both.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The question whether prenatal SSRI exposure is linked to autism spectrum disorders (ASD) in children remains inconclusive.
- Most of the case–control studies, and their pooled results in relevant meta-analyses, suggest an association.
- Some cohort studies, however, report negative or inconsistent findings and suggest confounding by indication.

WHAT THIS STUDY ADDS

- Data from cohort studies, exclusively, were pooled.
- Maternal psychiatric disorder but no SSRI exposure during pregnancy was also found to be associated with a significantly increased risk of ASD, as well as SSRI exposure.
- The similar effect sizes and largely overlapping confidence intervals make the previously suggested associations questionable.

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Introduction

The question whether selective serotonin reuptake inhibitor (SSRI) use during pregnancy is associated with the risk of autism spectrum disorders (ASD) in children has been an increasing focus of research in the last decade [1–18]. The statistically significant association between SSRI use during pregnancy and risk of ASD in children was demonstrated by several studies [1, 4, 10, 12], yet these results were challenged by the negative findings in some others [6, 9], raising the possibility of confounding by indication, which is the term used when the clinical indication (e.g. depression) for choosing a treatment (e.g. SSRI) also affects the measured outcome (e.g. ASD) [19]. There is still no conclusive answer even after the publication to-date of eight case–control studies [1–8], five cohort studies [9–13] and five meta-analyses [14–18].

In our recent previous meta-analysis of case–control studies, we demonstrated a significant association between SSRI exposure during the first (OR, 1.90; 95% CI 1.28–2.83), second (OR, 1.73; 95% CI 1.15–2.61) and anytime during pregnancy (OR, 1.66; 95% CI 1.23–2.23) and risk of ASD in children [17]. However, we also detected an unanticipated yet significant association with preconception-only SSRI exposure (use within the 3 months or 90 days prior to the last menstrual period (LMP) or estimated date of conception) with an effect size similar to the gestational exposure [17]. In addition, our qualitative review of the four cohort studies [9–13] yielded some inconsistent/negative findings, which further challenged and weakened the association that we detected in the meta-analysis of case–control studies. We suggested that a confounding by indication could not be ruled out [17].

The objective of this short report is to explore this suggestion with a meta-analysis pooling exclusively cohort studies by including the recently published data by Malm *et al*. [13]. This time we would like to test our previous hypothesis of confounding by indication through assessing whether the combined point estimate regarding the risk of ASD in children would suggest an association among the following three separate cohorts of pregnant women enrolled in cohort studies [9–13]: (1) pregnant women who discontinued SSRI until 3 months before pregnancy; (2) pregnant women who were exposed to SSRI during pregnancy; and (3) pregnant women with maternal psychiatric disorder but no exposure to SSRI during pregnancy.

Methods

Search strategy

The search strategy was described previously [17]. However, because the previous search was conducted from inception to 26 December 2015, we ran an additional search from 26 December 2015 to 4 February 2017 using the same strategy [17] in PubMed/MedLine, Cochrane Central Register of Controlled Trials and Reprotox®. No language or date restrictions were applied. The flow chart was prepared in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [20] and is presented in Figure 1.

Inclusion and exclusion criteria

Because we previously combined the data from the case–control studies [17], this time we only included the cohort studies investigating the link between prenatal exposure to SSRIs and ASD. A study was considered eligible if it met the following criteria: (1) a cohort of pregnant women with exposure to SSRIs any time during pregnancy was included; (2) a cohort of pregnant women who discontinued the SSRIs until 3 months before pregnancy or a cohort of pregnant women with maternal psychiatric disorder but no exposure to SSRIs during pregnancy was included; (3) a control (unexposed) group was included; (4) one of an odds ratio (OR), risk ratio (RR) or hazard ratio (HR) was reported; and (5) the data reported were not overlapping with another study. If an overlap between two studies was detected, the most recent one was included, after ensuring that both had similar methodological qualities. The exclusion criteria were case–control studies, case reports and series, animal studies, editorials and reviews.

Quality assessment

The Newcastle–Ottawa scale [21] was used for quality assessment of the study methodologies.

Outcome measures

The main outcome of interest for this meta-analysis was ASD.

Data extraction

Two authors (EK-A and SA) independently undertook the screening and data extraction process. The recently published data [13] were extracted using a standardized data extraction form and combined with our previously extracted data [17] and are presented in Table 1. Any disagreements were resolved by consulting with another author (YCK).

Meta-analytic methods

Point estimates (adjusted when available) were extracted from eligible cohort studies and combined using generic inverse variance method and random-effects model in RevMan 5.3 (Review Manager 5.3; Cochrane Collaboration, Oxford, UK) [22]. Heterogeneity was assessed utilizing the Q and I-square statistic. An I-square value between 25% and 50% signified low heterogeneity, between 50% and 75% moderate heterogeneity and >75% signified high heterogeneity [23]. Publication bias was not assessed because the number of included studies was less than 10 [24].

Results

Our search gleaned one additional cohort study by Malm *et al*. [13] published since our previous search. Because Boukhris *et al*. [12] did not report a point estimate consistent with our inclusion criteria, it was excluded. Four cohort studies were identified as eligible [9–11, 13]. The data from Hviid *et al*. [9] and Sorensen *et al*. [10] were largely overlapping. We chose to progress with Hviid *et al*. [9] in our primary analysis as it was methodologically superior and included

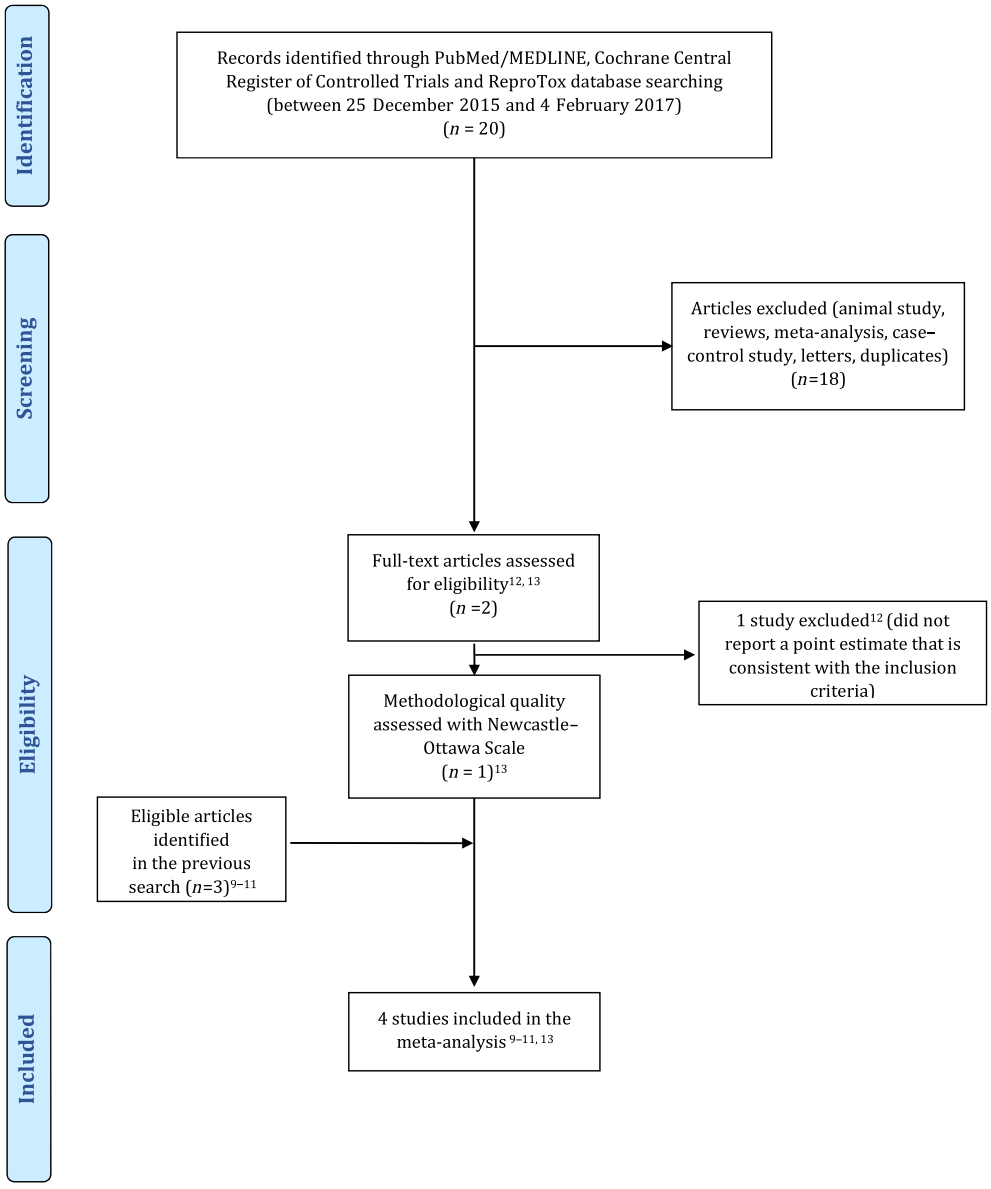


Figure 1
PRISMA flow diagram

an SSRI-discontinued group (use of SSRI starting from 2 years to 6 months before pregnancy) that is consistent with our inclusion criteria. However, we also extracted the point estimate of the SSRI-exposed group from the published data of Sorensen *et al*. [10] and retrieved the unpublished point estimate of the SSRI-discontinued group (use of SSRIs starting from 2 years to 6 months before pregnancy) from Sorensen *et al*. [10] through personal communication sensitivity analysis. Importantly, because El Marroun *et al*. did not measure and therefore did not provide an OR regarding ASD but did so regarding pervasive developmental problems (PDD), we extracted the OR regarding PDD (Model I) from this study [11]. Because the reported point estimates differed across the studies, the combined point estimates were reported either as HR, RR or OR with regard to the particular analysis.

Meta-analysis of cohort studies regarding SSRI-discontinuation until 3 months before pregnancy and risk of ASD in children

Three studies were eligible for this meta-analysis [9, 10, 13]. Hviid *et al*. [9] reported a cohort of pregnant women who discontinued SSRI until 6 months before pregnancy while Malm *et al*. [13] included a cohort of pregnant women who discontinued SSRI until 3 months before pregnancy. The discontinuation of SSRIs until 3 months before pregnancy was not significantly associated with an increased risk of ASD in

Table 1

Characteristics of the cohort studies considered for this review

	Hviid *et al.* 2013	Sorensen *et al.* 2013	El Marroun *et al.* 2014	Boukhris *et al.* 2015[a]	Malm *et al.* 2016
Country	Denmark	Denmark	Netherlands	Canada	Finland
Study period	1996–2005	1996–2006	2002–2006	1998–2009	1996–2010
Design/setting	Registry-based cohort	Registry-based cohort	Registry-based cohort	Registry-based cohort	Registry-based cohort
Data source	Danish National Prescription Registry, Danish Medical Birth Registry, Danish Psychiatric Central Register, Danish Civil Registration System	Danish National Prescription Registry, Danish Medical Birth Registry, Danish Psychiatric Central Register, Danish Civil Registration System, Danish National Hospital Register	Generation R Study Population-Based Cohort	Québec Pregnancy/ Children Cohort. Régiede l'assurance maladie du Québec, Québec centralized hospitalization archives databases, Public Prescription Drug Insurance database of Québec, Québec Statistics database	National Medical Birth Register, The Drug Reimbursement Register, The Hospital Discharge Register, National Population Register The Special Reimbursement Register
Number of participants	626 875	655 615	5976	145 456	845 345
Number of events					
SSRI-exposed:	Total: 6068 ASD: 52 Normal: 6016	Total: 7506 ASD: 91 Normal: 7415	Total: 69 ASD: Not reported Normal: Not reported	Total: 1583 ASD: 22 Normal: 1561	Total: 15 729 ASD: 88 Normal: 15 641
Unexposed:	Total: 620 807 ASD: 3752 Normal: 617 055	Total: 646 782 ASD: 5333 Normal: 641 449	Total: 5531 ASD: Not reported Normal: Not reported	Total: 142 924 ASD: 1023 Normal: 141 901	Total: 31 394 ASD: 100 Normal: 31 294
Inclusion criteria	Live births in Denmark between 1 January 1996 and 31 December 2005 Known gestational age Singleton births	Live births between 1 January 1996 and 31 December 2006 in the Danish Civil Registration System (CRS)	All pregnant women residing in Rotterdam; delivered between April 2002 and January 2006 Children participated in the pre- and postnatal follow-up and with information regarding behavioural and emotional problems	Live births between 1 January 1998 and 31 December 2009 All full-term (≥37 weeks' gestation) singleton infants whose mothers were covered by the Régiede l'assurance maladie du Québec drug plan for at least 12 months before and during pregnancy	Live births in Finland between 1 January 1996 and 31 December 2010Singleton births For outcome variables (depression, anxiety, autism spectrum disorder, attention-deficit/hyperactivity disorder) included only ICD codes after the diagnosis established
Exclusion criteria	Offspring with any of the following genetic conditions: fragile X syndrome, tuberous sclerosis, Angelman's syndrome, Down's syndrome, DiGeorge's syndrome, neurofibromatosis, and Prader–Willi syndrome) and congenital rubella syndrome	Children with missing or extreme values of gestational age (<23 weeks and >45 weeks) Missing information about the mothers Adopted children Children who died during the first year of life	If maternal SSRI use was unavailable If the use of SSRIs were before pregnancy only	Multiple pregnancies Preterm live births	Rett syndrome ICD codes which were used in the evaluation process Children with a depression diagnosis only during the first 2 years of life if the diagnosis was not recorded at later stages
Exposure	SSRIs; citalopram, fluoxetine, sertraline, paroxetine, escitalopram and fluvoxamine	SSRIs, TCA, SNRIs	SSRIs; paroxetine, fluoxetine, sertraline, fluvoxamine and citalopram	SSRIs, TCA, SNRIs, MAOI, other antidepressants; bupropion, amoxapine, maprotiline, mirtazapine, trazodone, and nefazodone	sertraline, fluvoxamine, escitalopram
Exposure time window	SSRIs with the ATC code N06AB that were filled	Women with antidepressant (ATC code	Exposure to SSRIs during pregnancy	AD exposure as having at least one prescription filled	At least one purchase of SSRIs during 1 year

(*continues*)

Table 1

(Continued)

	Hviid *et al.* 2013	Sorensen *et al.* 2013	El Marroun *et al.* 2014	Boukhris *et al.* 2015[a]	Malm *et al.* 2016
	during the period from 2 years before the beginning of the pregnancy until delivery	N06A) prescriptions from 30 days before conception to the day of birth		at any time during pregnancy or a prescription filled before pregnancy that overlapped the first day of gestation or prescription filled 1 year before first day of gestation	before pregnancy until 3 months before pregnancy and the period from 30 days before pregnancy until the end of pregnancy.
Control	Women with no SSRI prescriptions from 2 years before pregnancy through delivery	Women with no SSRI prescriptions from 30 days before conception to the day of birth	No exposure to SSRIs and a low score of maternal depressive symptoms by Brief Symptom Inventory	Infants with no *in utero* exposure to ADs	Women with no purchases of antidepressants or antipsychotics, and no depression or related psychiatric disorder at any time before or during pregnancy Two controls matched with one participant exposed to SSRI according to offspring date of birth within 6 months
Method of ASD diagnosis	International Classification of Diseases, 10th Revision (ICD-10)	International Classification of Diseases, 10th Revision (ICD-10)	Child Behaviour Checklist, Social Responsiveness Scale	International Classification of Diseases, Ninth Revision (ICD-9) OR International Classification of Diseases, 10th Revision	International Classification of Diseases, 10th Revision (ICD-10)
Covariates for adjustment	Age and calendar period, the mother's age at birth, country of origin, place of residence, parity, psychiatric diagnoses before delivery, other drug use during pregnancy, smoking status during pregnancy, employment status, and level of education	Maternal and paternal age at conception, parental psychiatric history (except maternal affective disorder), gestational age, birth weight, sex, and parity	Maternal age at intake, gender of the child, maternal education, ethnicity, maternal smoking habits and gestational age at birth	Use of ADs 1 year before the first day of gestation, use of ADs in the first trimester, infant sex and year of birth, and maternal variables; maternal age at first day of gestation, high school completed [≥12 y], recipient of social assistance, living alone, chronic or gestational hypertension, chronic or gestational diabetes, and other psychiatric disorders	Sex, maternal age, socioeconomic status, maternal history of other psychiatric diagnosis, entitlement to special reimbursement for chronic disease (ever), preterm birth, neonatal care unit
Results relevant to this meta-analysis	**SSRI discontinuation before pregnancy and the risk of autism:** Use of SSRI before pregnancy (2 year to 6 months) but not use during pregnancy aRR: 1.46; 95% CI (1.17–1.81) **SSRI exposure during pregnancy and the risk of autism:** Use of SSRIs during pregnancy but not before pregnancy a RR: 1.40; 95% CI (0.92–2.13) **Maternal psychiatric disorder but no SSRI exposure during pregnancy and the risk of autism:** N/A	**SSRI discontinuation before pregnancy and the risk of ASD:** Use of SSRI 180 days prior to conception a HR: 1.63; 95% CI (1.36–1.95) **SSRI exposure during pregnancy and the risk of ASD:** aHR: 1.6; 95% CI (1.3–2.0) **Maternal psychiatric disorder but no SSRI exposure during pregnancy and the risk of ASD:** N/A	**SSRI discontinuation before pregnancy and the risk of PDD:** N/A **SSRI exposure during pregnancy and the risk of PDD:** OR: 2.58; 95% CI (1.46–4.54) **Maternal psychiatric disorder but no SSRI exposure during pregnancy and the risk of PDD:** OR: 2.02; 95% CI (1.53–2.66)	**SSRI discontinuation before pregnancy and the risk of ASD:** N/A **SSRI exposure during pregnancy and the risk of ASD:** N/A for any time during pregnancy or first trimester, only available for the exposure during second and/or third trimester **Maternal psychiatric disorder but no SSRI exposure during pregnancy and the risk of ASD:** N/A	**SSRI discontinuation before pregnancy and the risk of ASD:** aHR: 1.08; 95%CI (0.74–1.56) **SSRI exposure during pregnancy and the risk of ASD:** aHR: 1.40; 95%CI (1.02–1.92) **Maternal psychiatric disorder but no SSRI exposure during pregnancy and the risk of ASD:** aHR:1.59; 95%CI (1.16–2.18)

(*continues*)

Table 1

(Continued)

	Hviid *et al.* 2013	Sorensen *et al.* 2013	El Marroun *et al.* 2014	Boukhris *et al.* 2015[a]	Malm *et al.* 2016
Quality assessment (Newcastle–Ottawa scale)	****/**/*** 9	****/**/*_* 8	****/**/_** 8	****/**/*_* 8	****/**/*-* 8

[a]Excluded for not including a point estimate consistent with our inclusion criteria.
AD: antidepressant; MAOI: monoamine-oxidase inhibitors; N/A: not available; PDD: pervasive developmental problems; SNRI: serotonin–norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressants.

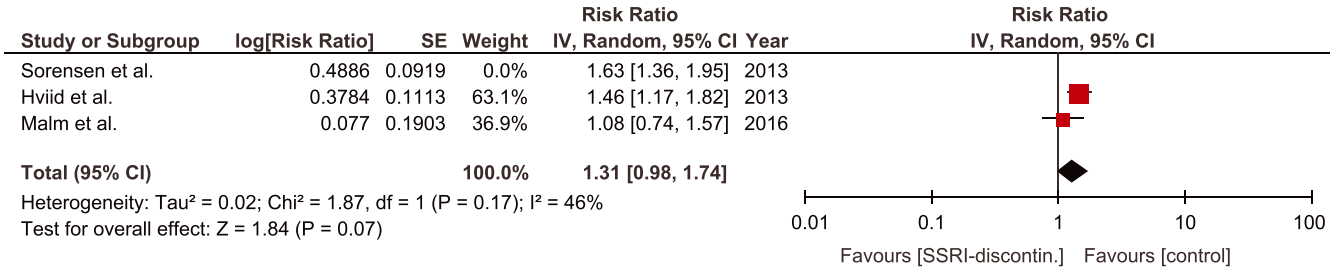
children when adjusted point estimate from each study was pooled (aRR, 1.31; 95% CI 0.98–1.74). No significant heterogeneity was detected among the studies (P = 0.17, I-square = 46%) (Figure 2A). The point estimate remained non-significant when Sorensen *et al.* [10] wsa included instead of Hviid *et al.* [9] with a non-significant moderate heterogeneity (aHR, 1.37; 95% CI 0.92–2.04; P = 0.051, I-square = 74%) (Figure 2B).

Meta-analysis of cohort studies regarding SSRI exposure during pregnancy and risk of ASD in children

Four studies were found eligible for this meta-analysis [9–11, 13]. The combined point estimate yielded a significant association between SSRI exposure during pregnancy and risk of ASD in children (aHR, 1.61; 95% CI 1.16–2.25). A low yet insignificant heterogeneity was detected among the studies (P = 0.15, I-square = 46%) (Figure 3A). The point estimate remained significant when Sorensen *et al.* [10] was included instead of Hviid *et al.* [9] (aHR, 1.65; 95% CI 1.28–2.11; P = 0.18, I-square = 41%, insignificant low heterogeneity) (Figure 3B).

Meta-analysis of cohort studies regarding maternal psychiatric disorder but no SSRI exposure during pregnancy and risk of ASD in children

Two studies were found eligible for this meta-analysis [11, 13]. We detected a significant association between maternal psychiatric disorder but no SSRI exposure during pregnancy and risk of ASD in children (aOR, 1.81; 95% CI 1.44–2.29). No significant heterogeneity was detected among the studies (P = 0.26, I-square = 20%) (Figure 4).



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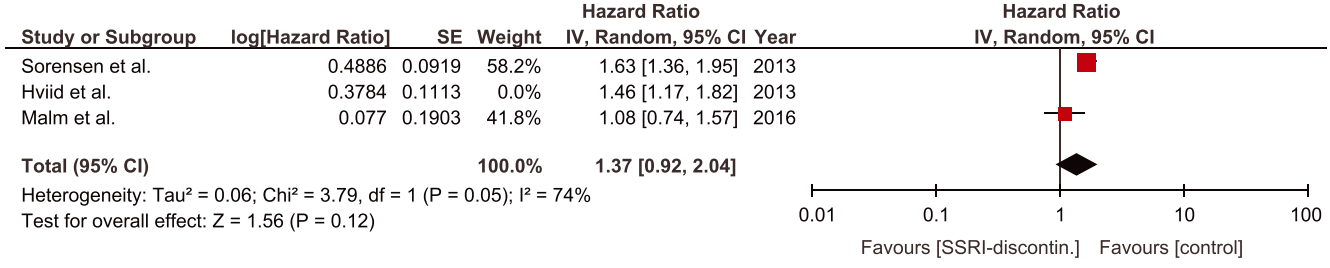
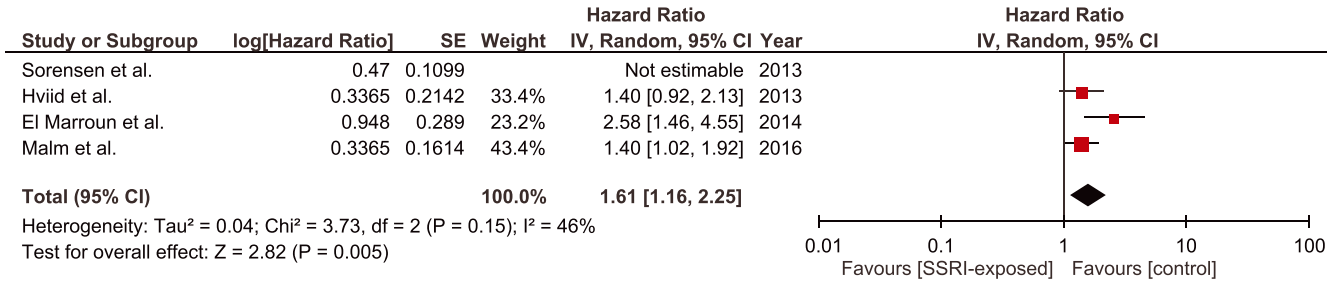


B

Figure 2

Meta-analysis of cohort studies regarding SSRI-discontinuation until 3 months before pregnancy and risk of ASD in children: (A) Forest plot of pooled adjusted risk ratios including Hviid *et al.* (B) Forest plot of pooled adjusted risk ratios including Sorensen *et al.*



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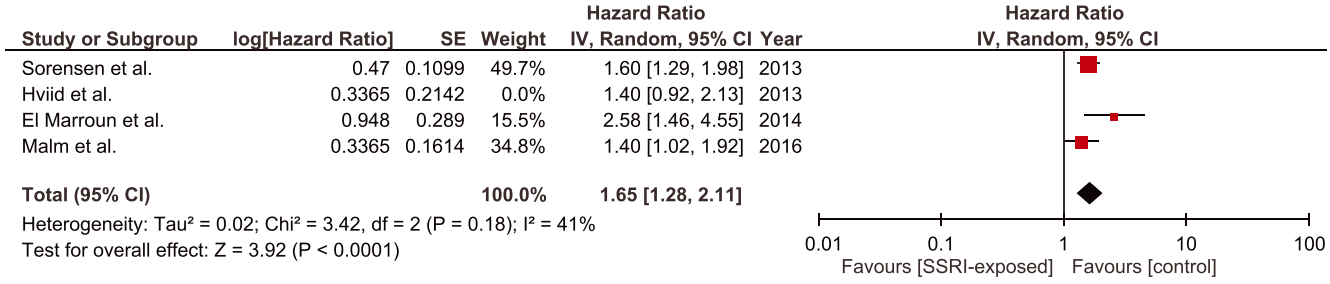

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Figure 3

Meta-analysis of cohort studies regarding SSRI exposure during pregnancy and risk of ASD in children: (A) Forest plot of pooled adjusted hazard ratios including Hviid *et al.* (B) Forest plot of pooled adjusted hazard ratios including Sorensen *et al.*

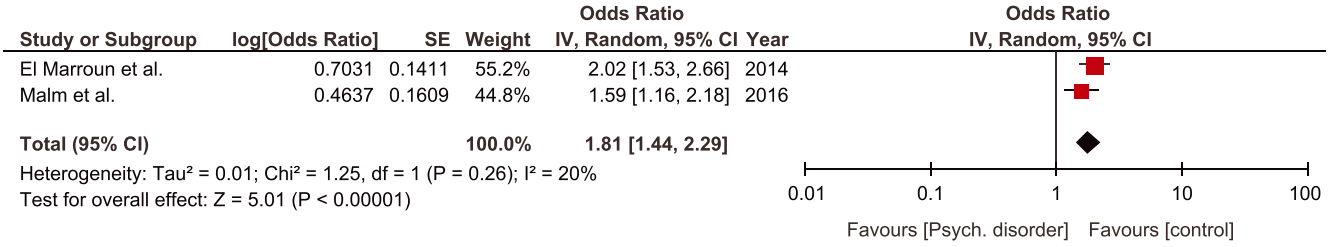

Figure 4

Meta-analysis of cohort studies regarding maternal psychiatric disorder but no SSRI exposure during pregnancy and risk of ASD in children. Forest plot of pooled adjusted odds ratios

Discussion

In this meta-analysis, both SSRI exposure any time during pregnancy and maternal psychiatric disorder but no SSRI exposure during pregnancy was demonstrated to be significantly associated with the risk of ASD in children. Although the combined point estimate for SSRI discontinuation until 3 months before pregnancy indicated a small increase in the risk of ASD, the trend was not significant.

The pooled effect size regarding SSRI exposure any time during pregnancy in this meta-analysis of cohort studies was very similar to the pooled effect size of SSRI exposure any time during pregnancy of the case–control studies we computed in our previous meta-analysis (aHR, 1.61; 95% CI 1.16–2.25 *vs*. aOR, 1.66; 95% CI 1.23–2.23) [17]. This effect size was also very close to the reported effect size in a recent meta-analysis investigating *in utero* SSRI exposure and the risk of ASD in children by Kobayashi *et al*. (aHR, 1.61; 95% CI 1.16–2.25 *vs*. aOR, 1.45; 95% CI 1.15–1.82) [16]. Nevertheless, Kobayashi *et al*. reported that this significant association did not persist when the analysis was restricted to the mothers with psychiatric disorders [16], which is also corroborated by the significant association we detected between maternal psychiatric disorder but no SSRI exposure during pregnancy and the risk of ASD in children in our meta-analysis. Of interest, in our meta-analysis, the pooled effect size in maternal psychiatric disorder but no SSRI exposure cohort regarding ASD risk in children was slightly bigger than that of the pooled effect size in SSRI exposure during pregnancy cohort (aOR, 1.81 *vs*. 1.61) and the CI of both effects sizes were largely overlapping (1.44–2.29 *vs*. 1.16–2.25). Our meta-analysis provides some advantages over the meta-

analysis by Kobayashi *et al*. [16] in terms of exclusively pooling cohort studies and comprising a recent cohort study [13] which was not available to them.

A combined summary of the findings of this and our previous meta-analysis [17] is as follows:

1. The pooled results of cohort studies in this meta-analysis suggest a trend for a mild increase in rişk of ASD with SSRI exposure until 3 months before pregnancy; however, it was not significant.
2. The pooled results of case–control studies suggest a significant association between preconception-only (within 3 months or 90 days prior to the LMP or estimated date of conception) SSRI exposure and risk of ASD in children [17].
3. The pooled results of case–control studies suggest a significant association between SSRI exposure during first, second trimester and anytime during pregnancy and risk of ASD in children [17], while pooled results of the cohort studies in this meta-analysis also suggest a significant moderate increase in risk of ASD with SSRI exposure at any time during pregnancy. The effect sizes were very similar.
4. The pooled results of the cohort studies in this study suggest a significant moderate increase in the risk of ASD with maternal psychiatric disorder but no exposure to SSRI during pregnancy with a slightly bigger effect size than that of SSRI exposure and with a largely overlapping confidence interval.

The most important limitation of our meta-analysis is the low number of included studies. Nevertheless, a major strength of our meta-analysis is the exclusive inclusion of cohort studies, which are less prone to bias in terms of assessing exposures during pregnancy. Our study is also the first meta-analysis to pool the point estimates of SSRI-discontinued and maternal psychiatric disorder but no SSRI exposure groups *vs*. SSRI exposure during pregnancy group.

In conclusion, this meta-analysis showed that maternal psychiatric disorder but no SSRI exposure is also associated with increased risk of ASD in children. The similar effect size of this group to that of SSRI exposure any time during pregnancy group with a largely overlapping confidence interval strengthens our previous suggestion that the maternal psychiatric disorder may be a strong confounder in studies assessing the connection between maternal SSRI use and ASD risk in children [17]. Although sought by an increasing number of studies and considered as biologically plausible [25–30], the suggested association of SSRI exposure during pregnancy and risk of ASD in children still remains to be adequately substantiated.

Competing Interests

All authors have completed the Unified Competing Interest Form (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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