Title:

Prenatal antidepressant exposure and the risk of attention-deficit hyperactivity disorder in children: A systematic review and meta-analysis

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Abstract: (164 words)

This systematic review assesses the association between prenatal antidepressant exposure and risk of ADHD in children. Electronic databases were searched up to 25 July 2017. Observational studies examining this association were included in the review and meta-analysis was conducted where appropriate. Eight relevant studies were identified. The seven studies included in the meta-analysis comprised a total of 2,886,502 children. The pooled estimates comparing prenatal exposure to non-exposure showed an adjusted rate ratio (aRR) of 1.39 (95%CI 1.21-1.61). Similarly, an increased risk was found comparing previous antidepressant users and non-users: aRR=1.56 (95%CI 1.25-1.95). The relationship between maternal psychiatric conditions and ADHD in children yielded an aRR of 1.90 (95%CI 1.47-2.45). Three studies conducted sibling-matched analyses with aRR of 0.94 (95%CI 0.75-1.16). These data suggest that the observed association between prenatal use of antidepressants and risk of ADHD in offspring can be partially explained by confounding by indication because the results from sibling-matched analyses do not support an increased risk of ADHD in discordant exposed siblings.

Keywords: Antidepressant; Pregnancy; Attention-Deficit/Hyperactivity Disorder.

Main Text:

1. Introduction

1.1 Depression and antidepressants use in pregnancy

Females are at higher risk of developing depression than males, particularly during pregnancy (Burke et al., 2005; Yonkers et al., 2009). Untreated depression during pregnancy has been associated with poor health outcomes for both mothers and children (Sontag-Padilla et al., 2013). The decision whether to use antidepressants during pregnancy is complex and requires that both clinician and patient consider the importance of reducing depressive symptoms, and the potential for adverse events affecting mother and child. Guidelines reflect this tension and generally recommend that antidepressants should be considered for pregnant women when it is judged that the benefits will outweigh the risk (Joint Formulary Committee, 2014; National Institute for Health and Clinical Excellence, 2007).

1.2 Attention-deficit/hyperactivity disorder (ADHD) in children

ADHD is a neurodevelopmental disorder in children and adolescents characterised by pervasive hyperactivity, persistent inattention and impulsiveness, and which impairs the lives of children (American Psychiatric Association, 2013). ADHD is common among school-aged children with a worldwide prevalence of approximately 5-7% (Polanczyk et al., 2014; Thomas et al., 2015). Rates of diagnosis exceed this epidemiological prevalence in North America and, whilst ADHD is under-diagnosed in most other parts of the world, rates of identified cases in other countries are increasing (Polanczyk et al., 2014). Due to the early onset, lifelong persistence, and high levels of associated comorbidities and impairment (Karam et al., 2015), the negative impact of ADHD on social outcomes, education and health of patients and their caregivers is significant (Fleck et al., 2015).

1.3 Prenatal antidepressants exposure and the risk of ADHD in children

Recent studies have suggested a potential link between maternal prenatal exposure to antidepressants, in particular, exposure to SSRIs, and the risk of ADHD in children (Boukhris et al., 2017; Castro et al., 2016; Clements et al., 2015; Figueroa, 2010; Laugesen et al., 2013; Malm et al., 2016; Man et al., 2017; Sujan et al., 2017). Previous meta-analyses and large-scale observational studies have also reported a possible association between prenatal exposure to antidepressants and autism spectrum disorder (ASD) in offspring (Man et al., 2015; Sujan et al., 2017). Given that both ADHD and ASD are major neurodevelopmental disorders in children and are sometimes concurrent (American Psychiatric Association, 2013), this adds to the concern about treating pregnant women with antidepressants and it is therefore important to determine whether prenatal exposure to antidepressant is an inherent risk factor for ADHD.

Selective serotonin reuptake inhibitors (SSRIs) are the most frequently prescribed class of antidepressants, both in general, and during pregnancy. Recent meta-analyses have suggested that SSRI exposure during pregnancy is associated with preterm birth and low birth weight (Huang et al., 2014), congenital malformation (Myles et al., 2013), and persistent pulmonary hypertension (Grigoriadis et al., 2014). Antidepressants cross not only the blood-brain barrier for intended pharmacological actions but also the placental barrier, and this could have unintended consequences for the developing foetus (Kendall-Tackett and Hale, 2010; Rampono et al., 2009). Animal studies have found that transient usage of fluoxetine during early development can result in abnormal emotional behaviour in adult mice, and this suggests a potential modulation of serotonin transporters during development of the brain systems involved in emotional and stress related responses (Ansorge et al., 2004). Pharmacokinetic and pharmacodynamic data, albeit indirect and somewhat weak, suggest a plausible biological mechanism between in-utero exposure to antidepressants and ADHD in children (Ansorge et al., 2004; Kendall-Tackett and Hale, 2010; Pedersen, 2017). Antidepressants primarily target

the monoamine neurotransmitters such as serotonin and norepinephrine; neuronal proliferation, migration and axonal wiring are modulated by monoamines (Pedersen, 2017). Furthermore, the use of antidepressants during pregnancy is associated with an increased risk of several birth defects and adverse birth outcomes (Grigoriadis et al., 2014; Huang et al., 2014; Louik et al., 2007; Myles et al., 2013), which may increase the risk of developing ADHD (National Institute for Health and Clinical Excellence, 2013). Placebo-controlled, randomised studies of the effects of maternal antidepressant use during pregnancy on the neurodevelopment of offspring are not feasible, and epidemiological studies therefore remain the most practical approach to investigating this association. Results from previous epidemiological studies are, however, inconsistent with contradictory findings (Boukhris et al., 2017; Castro et al., 2016; Clements et al., 2015; Figueroa, 2010; Laugesen et al., 2013; Malm et al., 2016; Man et al., 2017; Sujan et al., 2017). Evidence from most of the previous studies supports an association between prenatal antidepressant use and the risk of ADHD in children (Boukhris et al., 2017; Clements et al., 2015; Figueroa, 2010; Laugesen et al., 2013; Malm et al., 2016; Man et al., 2017; Sujan et al., 2017). However, some of these studies have emphasised that this association may be confounded by familial factors, and sibling-matched analyses do not support an increased risk (Laugesen et al., 2013; Man et al., 2017; Sujan et al., 2017). Further, those studies that used antidepressant exposure before pregnancy as a negative control also reported an increased risk for ADHD in offspring (Malm et al., 2016; Man et al., 2017; Sujan et al., 2017), suggesting that the observed increase in identified risk may have been confounded by maternal or familial factors. Given these conflicting results, it has been difficult to reach a consensus as to whether there is a link between antidepressant use in pregnancy and ADHD in children.

The possible link between prenatal antidepressant exposure and risk of neurodevelopmental disorders in childhood adds to the dilemma facing clinicians and patients in deciding how to manage severe affective disorders in women, both during pregnancy and at

the time that they are trying to conceive. There can be significant unfavourable outcomes in terms of withholding or terminating antidepressant medication abruptly during pregnancy. In view of these issues, we undertook a systematic review and meta-analysis of published observational studies to evaluate the association between antidepressant exposure during pregnancy and ADHD in children.

2. Methods

2.1 Systematic literature search

A systematic literature search was conducted using the search terms in Appendix 1. PubMed, EMBASE, PsycINFO and Cochrane Review database were searched up to 25 July 2017. Observational studies, including cohort and case-control study designs, which investigated the association between antidepressant use in pregnancy and ADHD in children were included. In addition, sibling-matched studies that compared the exposure and outcome status among siblings born to the same mother were also included. Sibling-matched analysis can be applied in both cohort and case-control settings that compare the risk of outcome between exposed sibling(s) to non-exposed sibling(s) in cohort design; or the odds of exposure between case sibling(s) to control sibling(s) in case-control design. Case reports, animal studies and conference abstracts were excluded. 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 identify additional relevant studies.

2.2 Quality assessment

As recommended by the Cochrane Collaboration (Higgins and Green, 2011), the methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale

(NOS) (Wells et al., 2000). Separate NOS criteria were used for case-control and cohort studies. A maximum of nine stars could be allocated for the following categories: selection (definition of cases/exposed subjects, representativeness of the cases/exposed subjects, selection of control/non-exposed subjects), comparability (controls or adjustment for confounding factors) and outcome/exposure (assessment/ascertainment of outcome/exposure, adequate non-response rate or follow-up time). The total score was obtained by adding the number of stars in the sub-categories where a higher score indicates better quality. Authors KM and WL independently graded all included studies using the NOS criteria.

2.3 Data extraction

Data from included studies were extracted using a standardised data collection form. Extracted data included study duration and design, data source, covariates, exposure groups, and sample size. Authors KM and WL independently extracted data and completed the characteristics form that was subsequently cross-matched to ensure consistency and accuracy. Outcome parameters such as rate ratio (RR), odds ratio (OR), hazard ratio (HR) 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 of developing ADHD in children following exposure to antidepressant, either at preconception (before pregnancy), or prenatal (during pregnancy). Definitions for “before pregnancy” and “during pregnancy” periods may vary between studies. The corresponding definition from each study were summarised if available.

2.4 Statistical analysis

Four pooled estimates of ADHD risk in children were evaluated from the meta-analysis: 1) Antidepressant use during pregnancy (prenatal user vs non-user); 2) Antidepressant use

before pregnancy (previous user vs non-user); 3) Psychiatric conditions in mothers during pregnancy (yes vs no); 4) Sibling-matched antidepressant use in pregnancy. Both the crude and the fully adjusted rate ratios (RRs) were pooled in the meta-analysis. As the studies included in the analysis were conducted 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. Higgins' I^2-statistic (Higgins and Green, 2011) was reported for each figure. The pooled estimates were calculated using DerSimonian and Laird's random-effects model (DerSimonian and Laird, 1986) to account for heterogeneity among studies. Analysis was performed on both the crude and adjusted estimates from the studies. The pooled estimates with 95% CI were calculated. Subgroup analysis was conducted by stratifying studies with different study designs. If more than one study shared the same data source, the meta-analysis only included one study from the same data source. Sensitivity analyses were performed by substituting these studies one by one. Post-hoc sensitivity analyses were conducted by restricting the analyses of 1) Prenatal exposure, 2) Pre-conception exposure, and 3) Maternal psychiatric conditions to studies explicitly stating that the three groups contained no overlapping individuals as we do not have information on the proportion of overlapping/non-overlapping groups in some of the studies. 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).

3. Results

3.1 Summary of literature

PubMed, EMBASE, PsycINFO and the Cochrane Review databases were searched; yielding 134, 309, 99 and 0 records respectively, with a total of 542 articles, from January 1946

to 25 July 2017. After the removal of duplicates, 431 records remained. Titles and abstracts were screened and full texts of relevant articles were retrieved for further review with 423 studies meeting the exclusion criteria. The systematic literature search returned eight observational studies (Figure 1) (Boukhris et al., 2017; Castro et al., 2016; Clements et al., 2015; Figueroa, 2010; Laugesen et al., 2013; Malm et al., 2016; Man et al., 2017; Sujan et al., 2017). All studies utilised electronic healthcare databases or national registries as data sources. Disease codes, such as International Classification of Diseases, Eighth, Ninth or Tenth (ICD-8, ICD-9 and ICD-10) were used to identify outcomes. Three studies were from the US (Castro et al., 2016; Clements et al., 2015; Figueroa, 2010), three from Nordic countries: Laugesen et al. from Denmark, Malm et al. from Finland and Sujan et al. from Sweden (Laugesen et al., 2013; Malm et al., 2016; Sujan et al., 2017), one from Canada (Boukhris et al., 2017), and one from Hong Kong (Man et al., 2017). Study commencement dates ranged from 1996 to 2001. A summary of the included studies is shown in 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 (eTable 1). Two included studies, Castro et al. (Castro et al., 2016) and Clements et al. (Clements et al., 2015) used the same data source. Clements et al. was used for the primary analysis as this included more subjects, and a sensitivity analysis was conducted by substituting Castro et al. for Clements et al. in the meta-analysis. Six other studies (five cohort studies, one case-control study) (Boukhris et al., 2017; Figueroa, 2010; Laugesen et al., 2013; Malm et al., 2016; Man et al., 2017; Sujan et al., 2017) were also eligible for the meta-analysis.

3.2 Antidepressant exposure during pregnancy (Prenatal exposure)

The seven studies entered into the meta-analysis included a total of 2,886,502 children (Boukhris et al., 2017; Clements et al., 2015; Figueroa, 2010; Laugesen et al., 2013; Malm et

al., 2016; Man et al., 2017; Sujan et al., 2017). Pregnancy period was defined by Boukhris et al., Clements et al., Castro et al. and Man et al. as any time between the last menstrual period and delivery, whereas Sujan et al. defined this as time from 90 days before estimated conception to delivery. Laugesen et al. and Malm et al defined pregnancy period as "30 days before pregnancy until the end of pregnancy" and Figueroa defined this as time between 279 days before delivery to date of delivery. The pooled estimates comparing prenatal users to non-users showed crude and adjusted RRs of 2.14 (95%CI 1.96-2.33) and 1.39 (95%CI 1.21-1.61), respectively (Figure 2a and eFigure 1a). Low heterogeneity was found between studies in the crude estimate (*Q*-statistics=8.44, p=0.21; I^2=29%) but high heterogeneity in the adjusted estimate (*Q*-statistics=30.1, p<0.01; I^2=80%).

The corresponding risk ratios in the first and second trimester were similar. The pooled adjusted RR in the first and second trimester were 1.26 (95%CI 1.01-1.57) and 1.42 (95%CI 1.18-1.73), respectively. However, the pooled adjusted RR in the third trimester was 1.05 (95%CI 0.74-1.48) (eFigure 2).

3.3 Antidepressant exposure before pregnancy (Pre-conception exposure)

Five studies provided information on antidepressant exposure before pregnancy and risk of ADHD in children (Clements et al., 2015; Figueroa, 2010; Malm et al., 2016; Man et al., 2017; Sujan et al., 2017). Slightly different definitions for "before pregnancy" were used for these studies. Clements et al., Castro et al. and Man et al. defined previous exposure as "any time before last menstrual period" whereas Sujan et al. defined before pregnancy as "between 270 and 90 days before estimated conception". Malm et al defined this as "one year before pregnancy until three months before pregnancy" and Figueroa defined this as "the year before pregnancy" (Table 1). Similar to the results for prenatal exposure, an increased risk was found when comparing previous antidepressant users and non-users: crude RR=2.20 (95%CI 1.75-

2.77), adjusted RR=1.56 (95%CI 1.25-1.95). Heterogeneity was significant for the crude estimate (Q-statistics=12.22, p=0.02; I^2=67%) and the adjusted estimate (Q-statistics=9.47, p=0.05; I^2=58%) (Figure 2b and eFigure 1b).

3.4 Maternal psychiatric conditions

The relationship between maternal psychiatric conditions and ADHD in children was evaluated in five studies (Boukhris et al., 2017; Clements et al., 2015; Figueroa, 2010; Malm et al., 2016; Man et al., 2017). Maternal psychiatric conditions during pregnancy yielded a pooled crude RR of 2.40 (95%CI 1.81-3.17) (*Q*-statistics=60.60, p<0.01; I^2=93%) and adjusted RR of 1.90 (95%CI 1.47-2.48) (*Q*-statistics=47.99, p<0.01; I^2=92%) (Figure 2c and eFigure 1c).

3.5 Sibling-matched antidepressant exposure during pregnancy

Three studies conducted sibling-matched analyses (Laugesen et al., 2013; Man et al., 2017; Sujan et al., 2017). The pooled RR of exposed sibling was 0.94 (95%CI 0.75-1.16) (Q-statistics=1.75, p=0.42; I^2=0%) (Figure 3).

3.6 Sensitivity Analyses

No material difference in the pooled estimates of any analyses were found when Clements et al. was replaced with Castro et al. (eFigure 3-5). The pooled estimates comparing prenatal users to non-users showed adjusted RRs of 1.34 (95%CI 1.17-1.54) (eFigure 3b). The corresponding pooled estimate for pre-conception exposure and maternal psychiatric conditions was 1.77 (95%CI 1.52-2.06) and 1.66 (95%CI 1.30-2.11) respectively (eFigure 4b and eFigure 5b).

Post-hoc sensitivity analyses were conducted by restricting the analyses of 1) Prenatal exposure, 2) Pre-conception exposure, and 3) Maternal psychiatric conditions to only those explicitly stating that the three groups contained no overlapping individuals (Malm et al., 2016; Man et al., 2017; Sujan et al., 2017). The pooled estimates comparing prenatal users to non-users showed adjusted RRs of 1.57 (95%CI 1.46-1.69). The corresponding pooled estimate for pre-conception exposure and maternal psychiatric conditions was 1.82 (95%CI 1.54-2.15) and 1.80 (95%CI 1.56-2.08), respectively (eTable 2). The results are similar to our original analyses.

4. Discussion

4.1 Summary of main results

To our knowledge, this is the first systematic review and meta-analysis of antidepressant use in pregnancy and the risk of ADHD in children. Previous population-based studies, with the exception of Castro et al., reported similar results with an increased risk of ADHD associated with prenatal exposure to antidepressants which ranged from 1.16 to 1.81 (Boukhris et al., 2017; Clements et al., 2015; Figueroa, 2010; Laugesen et al., 2013; Malm et al., 2016; Man et al., 2017; Sujan et al., 2017). Likewise, similar results were observed for pre-conception exposure to antidepressants with adjusted risk ratios ranging from 1.18 to 2.09 (Clements et al., 2015; Malm et al., 2016; Man et al., 2017; Sujan et al., 2017). There has been little biological explanation about why antidepressant exposure before pregnancy should result in ADHD in the offspring. Based on the effect of psychiatric disorder on ADHD and pre-conception exposure, it is likely that this increased risk may be partially explained by confounding due to pre-existing conditions.

4.2 Possibility of confounding by maternal psychiatric conditions

Indeed, previous studies have observed that maternal psychiatric conditions are risk factors for having ADHD offspring (Castro et al., 2016; Clements et al., 2015; Figueroa, 2010; Malm et al., 2016; Man et al., 2017). ADHD is highly heritable (Ronald et al., 2008; Smalley, 1997) and parents of children with ADHD are therefore more likely to suffer from ADHD. In recent years, it has become apparent that ADHD often persists into adulthood, and, when it does, it is associated with high levels of psychiatric comorbidity, including increased rates of depression and anxiety. However, it is also the case that most adults with ADHD are currently never properly diagnosed or treated (Asherson et al., 2012). Boukhris and colleagues (Boukhris et al., 2017) included maternal history of ADHD as a covariate in their analysis; however, only 186 out of 144,406 (0.13%) mothers had a record of ADHD diagnosis. This may explain why we found a possible link between psychiatric disorders in mothers and ADHD in children.

Confounding by genetic factors cannot be ruled out through population-wide comparisons. To address this, three studies investigated a within-family association (Laugesen et al., 2013; Man et al., 2017; Sujan et al., 2017). These same three studies further investigated this possibility through sibling-matched analyses (Laugesen et al., 2013; Man et al., 2017; Sujan et al., 2017), comparing exposure- and outcome-discordant offspring among siblings born to the same mother. All three analyses found no increased risk of ADHD in siblings with prenatal antidepressant exposure (pooled hazard ratio=0.94; 95%CI 0.75-1.16) (Laugesen et al., 2013; Man et al., 2017; Sujan et al., 2017). Sibling-matched design is useful in accounting for confounding of the exposure with all familial and environmental factors that are shared in common by the siblings, in particular genetic confounding (D'Onofrio et al., 2013). Clearly, there are differences between the results of population-based cohort studies and carefully controlled sibling cohort studies in our meta-analysis. The sibling-matched analyses are, in general, better regarded for controlling confounding factors at family level; such differences in methodology, as shown in our results, strongly support the argument that the association

between antidepressant use in pregnancy and ADHD in offspring is likely to be confounded by psychiatric disorders in the family or other environmental factors (unmeasured confounders), which cannot be controlled for in population-based cohort studies.

Nonetheless, we must acknowledge that sibling-matched studies require several assumptions. Sibling-comparison designs cannot rule out confounding factors that vary within siblings and that are highly correlated with both the exposure and the outcome such as maternal age (D'Onofrio et al., 2013; Sjolander and Zetterqvist, 2017). In addition, sibling comparisons are based on strict assumptions about carry-over effects (i.e. the possibility that exposure of a sibling influences the outcome of another) (Lahey and D'Onofrio, 2010).

4.4 Other study designs that address potential confounding effects

With respect to the limitations of the sibling-matched design, some of the included studies provided alternative analyses that addressed for confounding effect in this association. Two studies compared mothers who continued antidepressants during pregnancy with those who discontinued antidepressants prior to becoming pregnant (Man et al., 2017; Sujan et al., 2017). Man et al. (Man et al., 2017) conducted direct comparison between the continuing users and users who discontinued with HR=0.75 (95%CI 0.51-1.10). On the other hand, Sujan et al. (Sujan et al., 2017) investigated whether the risk estimate for continuing users and the discontinued users was statistically different from each other. They found no significant difference between the two groups (p-value=0.49) which suggests no increased risk of ADHD. In addition, Man et al. (Man et al., 2017) used maternal antipsychotic treatment as an active comparator to antidepressants. As confounding by indication is likely to be an important issue in this association, comparing individuals with treatment to those without treatment may induce bias (Schneeweiss et al., 2007). By comparing gestational use of antidepressants to gestational use of antipsychotics, Man et al. found no difference in the risk of ADHD between these groups

(hazard ratio=1.27, 95%CI 0.73-2.18) which support the argument of confounding by indication. Sujan et al. (Sujan et al., 2017) applied a negative control analysis by considering antidepressant exposure in fathers during the childbearing period of their partner. Interestingly, an increased risk of ADHD in offspring was identified when fathers were exposed to antidepressants during the pregnancy of their partners (hazard ratio=1.73, 95%CI 1.38-2.17) (Sujan et al., 2017). As the medication in the father has no biological contact with the foetus, this finding supports the argument that the observed association is confounded by non-pharmacological factors. The findings suggest that the observed association is likely to be affected by unmeasured confounding factors within the family, such as family health conditions and genetic factor.

4.5 Availability of data sources and methodological challenges in previous studies

Few studies have investigated the association between antidepressant use in pregnancy and the risk of ADHD in children. This may reflect the complexities involved in designing and conducting this type of study. Interventional studies are not deemed to be ethical in the clinical setting, and therefore observational studies appear to be the only practical way to investigate these associations. However, obtaining a large sample size in non-database studies remains challenging, and achieving long term follow-up in the cohort setting, together with recall bias in the case-control setting are major methodological limitations to carrying out such studies and drawing unbiased conclusions about the findings. Now that data linkage between mother and child data is becoming more common, further large scale database studies, preferably with sibling-matched analyses, are warranted to address these potential associations.

Castro et al. and Clements et al. obtained their study sample from the same data source using similar methodologies but reported different results (Castro et al., 2016; Clements et al., 2015). When compared with Clements et al., Castro et al. used a different matching criteria

resulting in a smaller sample size (5,498 in Castro et al., 7,874 in Clements et al.) and a less precise estimate (adjusted odds ratio=0.97, 95%CI 0.56-1.69).

4.6 Clinical implications

It is important to emphasise that antidepressants should not be stopped abruptly or withheld during pregnancy due to concerns about the risk of ADHD in the offspring. This could lead to maternal depression deteriorating. Untreated pregnant women with depression are more at risk of developing postpartum depression and suicidality (Andersson et al., 2004). The negative consequences of untreated maternal depression might also affect the child's development and higher impulsivity, maladaptive social interactions, and cognitive, behavioural, and emotional difficulties have been shown to occur (Bennett et al., 2004; Bonari et al., 2004). Our study has shown that for mothers who had either taken antidepressants during pregnancy or only before pregnancy, the risk of ADHD among their children was similar. Therefore, in view of the current evidence, pregnant women should not stop treatment due to concerns of ADHD in their children.

4.7 Strengths and limitations

We undertook a rigorous systematic review and meta-analysis which included all relevant literature to date. Reviewer selection bias was minimised by using a predefined search strategy for selection and data extraction was conducted by two independent authors. All included studies were conducted with large databases which provided a relatively large sample size for the studies.

Differences in study designs, exclusion criteria, control groups selection, duration of follow-up, exposure definitions, outcome definitions, included covariates and analysis model can affect the accuracy of pooled estimates for both crude and adjusted ORs. In addition, how

pregnancy information is stored and retrieved in each study database, may explain the different study designs and definitions. We observed low heterogeneity in the crude pooled estimate but high heterogeneity in the adjusted pooled estimate. This may represent the difference in the analysis for each study, in particular, which covariates were included, and what analysis model was used, therefore, results with high heterogeneity should be interpreted with caution. However, all studies were essentially measuring the same outcomes and there is no indication of large clinical heterogeneity to invalidate our meta-analysis. More importantly, the forest plots of all analyses are consistent and the conclusions are consistent with biological plausibility; thus, we believe it is appropriate to numerically summarise all results in this systematic review.

Our meta-analysis included three main comparisons: mothers exposed during pregnancy, mothers exposed before pregnancy, and mothers with psychiatric conditions. Just three of the included studies (Malm et al., 2016; Man et al., 2017; Sujan et al., 2017), stated clearly that there was no overlapping individuals in these groups, whilst this was not clear for the other included studies. However, all studies provided adjusted estimates for the three groups. For example, the adjusted estimate for "prenatal exposure" was adjusted for previous exposure and/or maternal psychiatric conditions. The different methodological approaches of the included studies are reflected in the heterogeneity index. Nevertheless, the results were similar to the original analysis in the post-hoc sensitivity analyses by restricting the analyses to Malm et al., Man et al. and Sujan et al. Thus, we believe this would not alter our study conclusion.

Only two studies (Figueroa, 2010; Man et al., 2017) restricted their sample to children who were at least five years old at the time of assessment whereas the others did not apply any age constraints up to five years old (Boukhris et al., 2017; Castro et al., 2016; Clements et al.,

2015; Laugesen et al., 2013; Malm et al., 2016; Sujan et al., 2017). As ADHD is much less likely to be diagnosed clinically before the age of five years, these studies may have identified unrepresentative samples with significant proportions of children under age five, leading to biased estimates of the actual risk.

In addition, all studies relied on a clinical diagnosis of ADHD being made (Castro et al., 2016; Clements et al., 2015; Figueroa, 2010; Laugesen et al., 2013; Malm et al., 2016; Sujan et al., 2017). This may impact differently on individual study results with possibly different diagnostic criteria or different local practices that consequently affect the pooled estimates. We could only estimate the prevalence of ADHD in the cohort studies (Boukhris et al., 2017; Laugesen et al., 2013; Malm et al., 2016; Man et al., 2017; Sujan et al., 2017). The prevalence of ADHD in the Scandinavian studies ranged from 0.6% to 2.1%, this was 3.2% in the Canada study and 3% in the Hong Kong study. All are lower than the rate in epidemiological studies which suggest a global prevalence of around 5% (Polanczyk et al., 2014). A low prevalence of ADHD in the Scandinavian studies may be due to the inclusion of children aged under 5 years and may also be due to the nature of register-based studies where only clinically detected cases are included. This is a limitation that applies to all of the included studies. Under-diagnosis of less severe ADHD cases in control groups could account for outcome misclassification that would bias the estimates towards null; hence, we may have underestimated the actual risk but this is unlikely to affect the conclusion.

As the number of studies included in the meta-analysis was limited, a funnel plot was not performed and it was not possible to assess for publication bias. In addition, the studies identified for meta-analysis are all relatively recent (2010-2017) and present similar results. We cannot, therefore, exclude the possibility of publication bias. As a result, the pooled estimates may be overestimated.

5. Conclusions

In conclusion, in this systematic review and the meta-analysis of existing studies, although an increased risk of ADHD in the offspring of mothers treated with antidepressant during pregnancy was observed, maternal exposure to antidepressants before pregnancy, as well as mothers being diagnosed with a psychiatric disorder, showed similar results. Similarly, sibling-matched studies do not support an increased risk of ADHD in the offspring of mothers treated with antidepressants during pregnancy. Therefore, it can be concluded that the association of ADHD in offspring with maternal prenatal antidepressant exposure is likely to be confounded by other factors.

Competing Interests:

We have read and understood the policy on declaration of interests and declare the following interests: Dr. Esther Chan reports grants from Janssen (a division of Johnson & Johnson), BMS, Pfizer, The Research Grants Council (RGC, Hong Kong), received for other work. Prof. Coghill reports grants from The European Union FP7 Programme and Shire, and honoraria from Shire, Eli Lilly, Novartis and Janssen-Cilag, acted as an advisor to Shire and Lundbeck and received royalties from Oxford University Press. Prof. Coghill was a member of British Association for Psychopharmacology ADHD, Depression and Bipolar disorder guideline groups. Prof. Simonoff reports grants from Innovative Medicines Initiative (IMI), National Institute for Health Research Program Grant for Applied Research and the NIHR Biomedical Research Centre for Mental Health. Dr Ip reports grants from the Research Grants Council (RGC, Hong Kong) and the Health and Medical Research Fund (Food and Health Bureau, Hong Kong). Prof. Wong reports grants from The Research Grants Council (RGC, Hong Kong), Innovative Medicines Initiative (IMI), Shire, Janssen-Cilag, Eli-Lily, Pfizer,

European Union FP7 Programme, outside the submitted work. Prof. Wong is a member of the National Institute for Health and Clinical Excellence (NICE) ADHD Guideline Group and was a member of the British Association for Psychopharmacology ADHD Guideline Group and acted as an advisor to Shire. Dr Phyllis Chan acted as an advisor to Eli Lilly. Prof Sturkenboom is leading a research group that received grants for specific post-authorisation safety projects from Novartis, Boehringer, GSK and Servier, none related to this topic. Dr Schuemie is a full-time employee and shareholder of Johnson & Johnson. Other authors report no competing interests; no other relationships or activities have been declared that could appear to have influenced the submitted work.

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Figure and Tables

Table 1: Summary of included studies

Study	Data Source	Study period	Country	Case definition	Exclusion criteria	Selection of comparison group	Exposure duration definition
Boukhris 2017	Data from the Quebec Pregnancy/Children Cohort (QPC) with linkage to three administrative databases: the Regie de l'assurance maladie du Quebec (RAMQ), Quebec's Public Prescription Drug Insurance database, and the Quebec hospitalisation archive (MedEcho) database.	1998-2009	Canada	All children with a diagnosis of ADHD or at least one prescription filled for ADHD medications between birth and the end of follow-up. ADHD diagnosis was defined as a medical service claim or hospitalisation with a diagnosis of ADHD according to ICD-9 codes: 314; ICD-10:F90	All births that were not full-term birth (<37 weeks of gestation); non-singleton birth; children with autism spectrum disorder; or mothers who were not covered for at least 12 months in the database were excluded.	Women without antidepressants prescriptions	Exposures were identified from RAMQ prescription database. At least one prescription filled at any time during pregnancy or a prescription filled before pregnancy that overlapped the first day of gestation
Castro 2016	Three independent electronic health records: the Partners HealthCare system, which spans Massachusetts General Hospital (MGH), Brigham and Women's Hospital and Newton-Wellesley Hospital, as well as affiliated outpatient clinics; the Beth Israel Deaconess Medical Center (BIDMC); and the Boston Children's Hospital.	1997-2010	United States	Children age 2 -19 years with at least one ICD-9 code of 314.x and no ICD-9 code of 299 between 1997 and 2010, delivered at MGH, Brigham and Women's Hospital, Newton-Wellesley Hospital or BIDMC.	If mother -child matches could not be confirmed, those pairs were omitted from analysis. Restricted the analysis to one child per mother, choosing the child with ADHD when a mother had both a case and control offspring. When two	Children were then matched 1:3 with healthy control children delivered at MGH, Brigham and Women's Hospital, Newton-Wellesley Hospital or BIDMC with the same year of birth, birth hospital, sex, insurance type as a proxy for socioeconomic status, race/ethnicity and	Exposures were identified using e-prescribing data in the EHR, both inpatient and outpatient, which record number of pills, frequency and refill number, allowing calculation of exposure period. Previous exposure defined as exposure at any time before

	Additional maternal and paternal data, as well as confirmation of matching accuracy between mothers and offspring were obtained from the Massachusetts Registry of Vital Records and Statistics.				case or two control children were identified from one mother we randomly selected one child for inclusion in the study.	preterm versus full-term status. Children with any history of ASD, ADHD or intellectual disability (ICD-9 of 299, 314 or 317 -319) were excluded from the control population. If fewer than three matches could be identified for a case, year of birth was relaxed so that controls were born within 3 years of a given case.	last menstrual period.
Clements 2015	Three independent electronic health records: the Partners HealthCare system, which spans Massachusetts General Hospital (MGH), Brigham and Women's Hospital and Newton-Wellesley Hospital, as well as affiliated outpatient clinics; the Beth Israel Deaconess Medical Center (BIDMC); and the Boston Children's Hospital. Additional maternal and paternal data, as well as confirmation of matching accuracy between mothers and offspring were obtained from the Massachusetts	1997-2010	United States	Children age 2 -19 years with at least one ICD-9 code of 314.x and no ICD-9 code of 299 between 1997 and 2010, delivered at MGH, Brigham and Women's Hospital, Newton-Wellesley Hospital or BIDMC.	If mother -child matches could not be confirmed, those pairs were omitted from analysis. Restricted the analysis to one child per mother, choosing the child with ADHD when a mother had both a case and control offspring. When two case or two control children were identified from one mother we randomly selected one child for inclusion in the study.	Children were then matched 1:3 with healthy control children delivered at MGH, Brigham and Women's Hospital, Newton-Wellesley Hospital or BIDMC with the same year of birth, birth hospital, sex, insurance type as a proxy for socioeconomic status, race/ethnicity and preterm versus full-term status. Children with any history of ASD, ADHD or intellectual disability (ICD-9 of 299, 314 or 317 -319) were excluded from the control	Exposures were identified using e-prescribing data in the EHR, both inpatient and outpatient, which record number of pills, frequency and refill number, allowing calculation of exposure period. Previous exposure defined as exposure at any time before last menstrual period.

	Registry of Vital Records and Statistics.					population. If fewer than three matches could be identified for a case, year of birth was relaxed so that controls were born within 3 years of a given case.	
Figueroa 2010	MarketScan data, collected by Thompson Reuters (previously Medstat), are obtained from large self-insured employers from all states, except Alaska and Hawaii.	1996-2006	United States	Live born who were born during 1997–2002 to mothers aged 15 to 50 years. Only the first delivery was included. Delivery hospitalizations were identified by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes V27 and 650, by diagnosis-related group codes 370 to 375	Excluding any ICD-9-CM codes incompatible with a live delivery (e.g., abortion, ectopic pregnancy; i.e., 630–639). All children whose length of observation was less than 4years after the delivery date were excluded.	Children without claims with a primary or secondary diagnosis of ADHD and prescription claims for stimulants	National drug coding numbers were used to identify specific medications. Antidepressants were grouped by their mechanism of action into 3 groups: selective serotonin reuptake inhibitors, bupropion, and other antidepressants (tricyclics, tetracyclics, mirtazapine, and venlafaxine). Exposure before pregnancy defined as any exposure in the year before pregnancy.
Laugesen 2013	Danish Medical Birth Registry; Danish National Prescription Registry; Danish Psychiatric Central Register; Danish Civil Registration	1996-2009	Denmark	All singletons born alive from 1996 until the end of 2009. ADHD was detected either as a diagnosis of ADHD or redemption of a	Patients with missing data were excluded from the analyses	Women without antidepressants prescriptions from 30 days before conception to the day of birth	In utero exposure to antidepressants was defined as maternal redemption of a prescription for an antidepressant

	System; Danish National Hospital Register			prescription for ADHD medication			30 days prior to or during pregnancy, as identified through the Danish National Prescription Registry
Malm 2016	Finland Medical Birth Register, the Register of Congenital Malformations, the Hospital Discharge Register including inpatient and outpatient data, the Drug Reimbursement Register, and the Population Register	1996-2010	Finland	Singleton live births in Finland between January 1, 1996, and December 31, 2010	Excluded individuals with a depression diagnosis only during the first 2 years of life if the diagnosis was not recorded at later stages.	Mothers without SSRI prescriptions	Mothers in the SSRI exposed group had 1 or more purchases of SSRIs during the period from 30 days before pregnancy until the end of pregnancy. Exposure before pregnancy defined as exposure at one year before pregnancy until three months before pregnancy
Man 2017	Data from Hong Kong Clinical Data Analysis and Reporting System that includes electronic health record in all public hospitals and their associated ambulatory clinics	2001-2015	Hong Kong	Liveborn children with an ADHD diagnosis, registered as ICD-9-CM diagnosis code 314, or a prescription for an ADHD drug, namely methylphenidate or atomoxetine	Children with: missing mother-child link; perinatal death; abortion case; missing gestation week; missing gender; missing Apgar score at 1 minute or 5 minute; date of conception outside study period, were removed	Children with mothers who did not have antidepressant exposure during pregnancy	Antidepressant use in mothers was extracted from the prescribing and dispensing records in CDARS. All drugs in the British National Formulary chapter 4.3 were included. Previous exposure defined as exposure at any time before last menstrual period.
Sujan 2017	Swedish registries: the Multi-Generation Register; the Prescribed Drug Register;	1996-2012	Sweden	Children with first diagnosis of ADHD, which were identified	Cases of multiple births, those with a missing father	Children with mothers who did not have	Main exposure evaluated were first trimester exposure to any antidepressants.

	Medical Birth Register; National Patient Register; National Crime Register; Swedish Register of Education			using inpatient and outpatient diagnoses made by specialists according to ICD-9 and ICD-10.	identifier, missing invalid response on covariates, and missing the small for gestational age variable were excluded.	antidepressant exposure in the first trimester.	With Anatomical Therapeutic Chemical Classification (ATC) codes beginning with N06A. Exposure before pregnancy defined as exposure between 270 and 90 days before estimated conception.

Table 2: Summary of included studies' results

Study	Number of participants	Number of events	Crude OR[a]/RR[b]/HR[c]	Factors considered during adjusted analysis	Adjusted OR/RR/HR
Boukhris 2017	144,406	Antidepressants group: 267 with ADHD; 4411 without ADHD Unexposed group: 4297 with ADHD; 135431 without ADHD	1.86[e] (95% CI 1.65-2.09)	Gender, birth year, maternal age, maternal education level, recipient of social assistance, area of residence, maternal psychiatric disorders in the year prior to or during pregnancy (depression/anxiety, other psychiatric disorders), maternal co-morbities (gestational diabetes, gestational hypertension), maternal history of ADHD	1.20 (95% CI 1.00-1.40)
Castro 2016	5,498	ADHD group: 29 with antidepressant; 1672 without antidepressant Control group: 57 with exposure; 3740 without exposure	0.91 (95% CI[d] 0.56-1.42)	Gender, race, birth year, insurance type, median income tertile, past history of maternal depression	0.97 (95% CI 0.53-1.69)
Clements 2015	7,874	ADHD group: 63 with antidepressant; 2180 without antidepressant Control group: 68 with antidepressant; 5563 without antidepressant	2.30 (95% CI 1.62-3.24)	Gender, race, birth year, insurance type, median income tertile, past history of maternal depression	1.81 (95% CI 1.22-2.70)
Figueroa 2010	38,074	ADHD group: 23 with SSRI, 5 with Bupropion, 1 with other antidepressant; 402 without antidepressant Control group: 893 with SSRI, 109 with Bupropion, 118 with other antidepressant; 36925 without antidepressant	2.35[e] (95% CI 1.61-3.45)	Maternal age group, gender of the child, urban or rural metropolitan statistical area, year of birth, age at last claim and at end of eligibility, maternal and paternal mental health diagnoses, the presence or absence of maternal mental health-related visits by period of time, the use of other psychotropics during pregnancy, and perinatal complications	1.16[e] (95% CI 0.72-1.90)
Laugesen 2013	877,778	Antidepressants group: 432[e] with ADHD, 14576[e] without ADHD	2.00	Gender of the child, calendar time at birth, birth order, maternal age at birth, maternal smoking status, maternal psychiatric diagnoses, paternal psychiatric diagnoses,	1.20

		Unexposed group: 12409[e] with ADHD, 850361[e] without ADHD	(95% CI 1.70-2.30)	maternal diseases during pregnancy (infections, epilepsy) and maternal anxiolytics/hypnotics/sedatives use during pregnancy	(95% CI 1.10-1.40)
Malm 2016	47,123	SSRIs group: 160 with ADHD; 15569 without ADHD Unexposed group: 124 with ADHD; 31270 without ADHD	2.62 (95% CI 2.06-3.34)	Sex; socioeconomic status; smoking during pregnancy; neonatal care unit; maternal history of other psychiatric diagnosis; maternal history of substance abuse; paternal history of psychiatric diagnosis; parental death	1.66 (95% CI 1.27-2.16)
Man 2017	190,618	Antidepressant group: 74 with ADHD; 1,178 without ADHD Unexposed group: 5,585 with ADHD; 183,781 without ADHD	2.26 (95%CI 1.80-2.84)	Maternal age at delivery, infant's sex, birth year, birth hospital, parity, maternal underlying medical conditions before delivery (pre-existing diabetes, epilepsy, gestational diabetes, psychiatric conditions, hypertension), use of other psychotropic drugs (antipsychotics, British National Formulary chapter 4.2.1, 4.2.2), and socioeconomic status.	1.39 (95%CI 1.07-1.82)
Sujan 2017	1,580,629	Antidepressant group:613 with ADHD; 21931 without ADHD Unexposed group: 32311 with ADHD; 1525774 without ADHD	2.21 (95%CI 2.04-2.39)	Parity; year of birth; country of birth; age at childbearing; highest level of completed education; history of any criminal conviction; history of severe psychiatric illnesses (inpatient diagnosis of ICD-8, ICD-9, or ICD-10 schizophrenia, bipolar disorder, or other non-drug-induced psychoses); and history of any suicide attempts.	1.58 (95% CI 1.46-1.71)

[a]OR=Odds Ratio

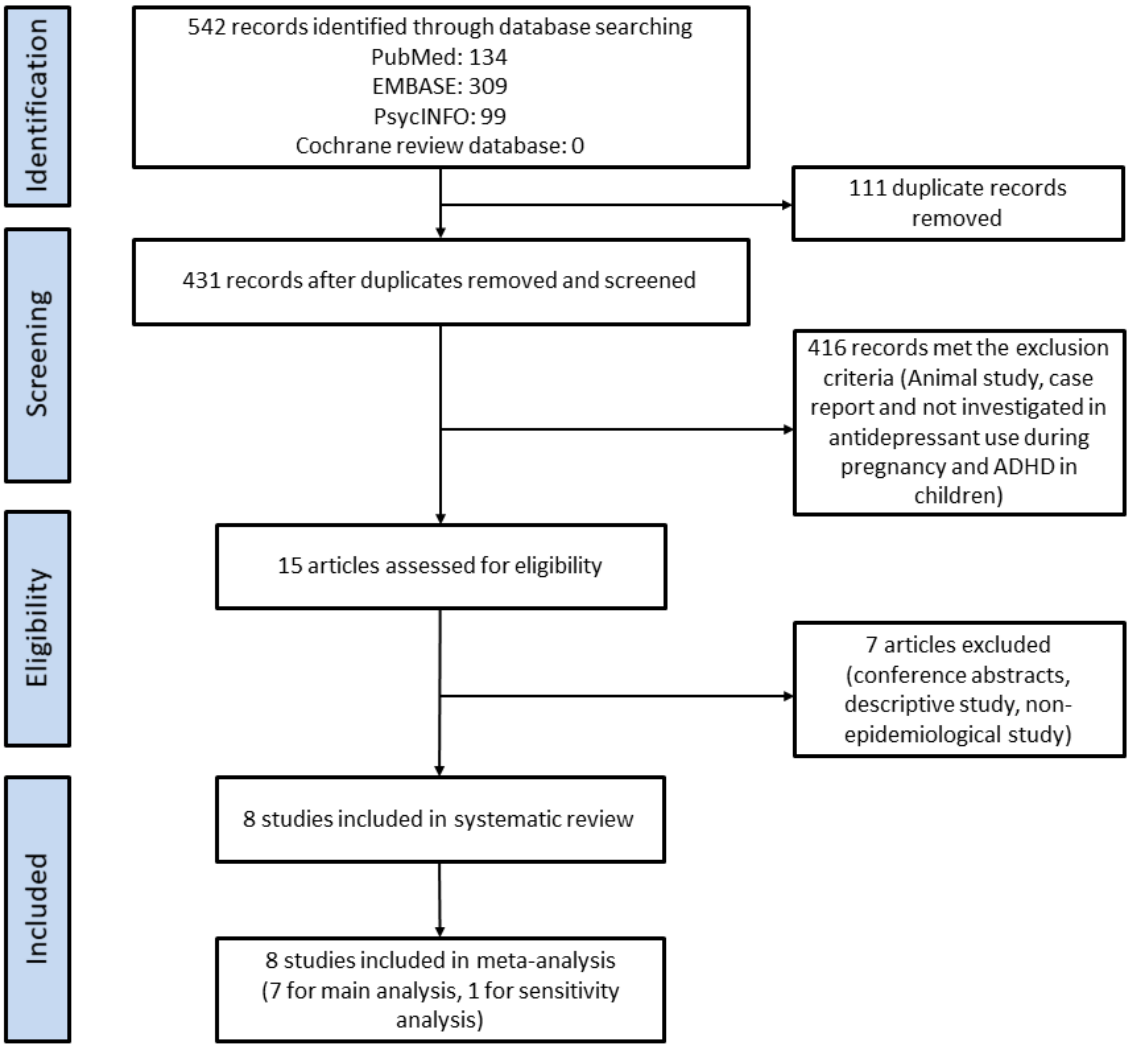
[b]RR=Rate Ratio,

[c]HR=Hazard Ratio

[d]95% CI=95% confidence interval

[e]Figures were not directly available, calculated by the figures given in the study

Figure 1: Flowchart for studies inclusion



Abbreviations: ADHD=Attention deficit/hyperactivity disorder.

Figure 2a: Prenatal antidepressant user vs non-user (adjusted estimate)

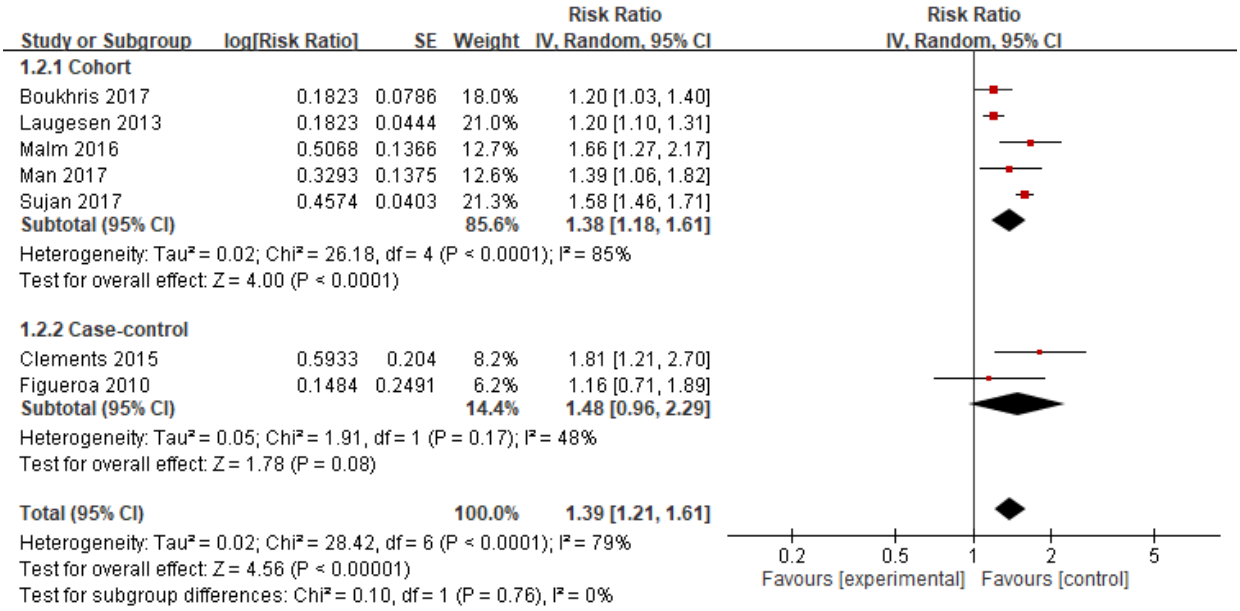


Figure 2b: Previous antidepressant user vs non-user (adjusted estimate)

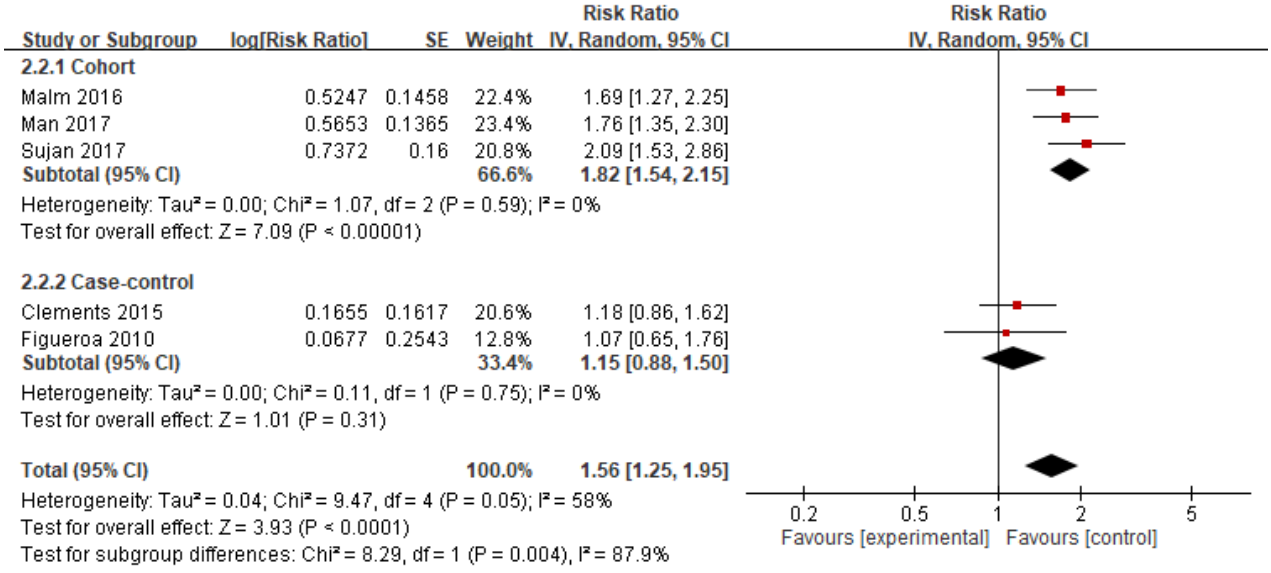


Figure 2c: Maternal psychiatric conditions (adjusted estimate)

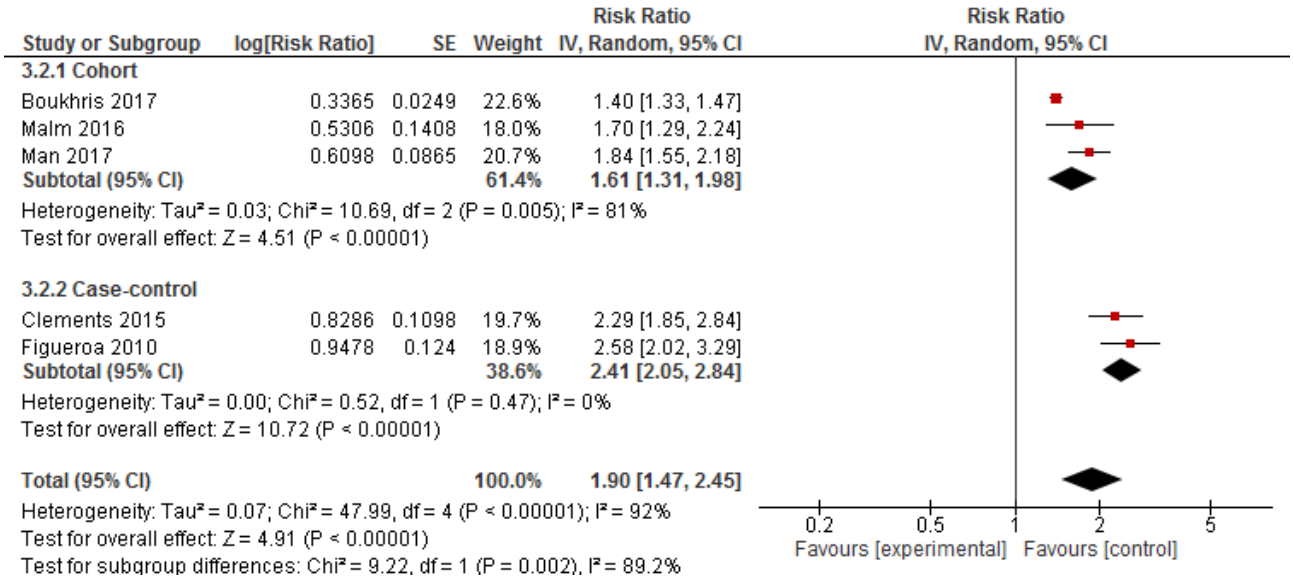


Figure 3: Forest plot of the sibling-matched analysis