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Prenatal antidepressant exposure and the risk of attention-deficit hyperactivity disorder: A population based cohort study and meta-analysis

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Abstract (321words)

OBJECTIVE: To assess the potential association between prenatal exposure to antidepressants and the risk of attention-deficit hyperactivity disorder (ADHD).

DESIGN: Population based cohort study and meta-analysis

SETTING: Data from the Hong Kong population-based electronic medical records on the Clinical Data Analysis & Reporting System.

PARTICIPANTS: Pregnant women who were living in Hong Kong and gave birth in public hospitals between January 2001 and December 2009. Children were followed up to December 2015.

MAIN OUTCOME MEASURES: Hazard ratio of antidepressant exposure during pregnancy and ADHD in children aged 6 to 14 with an average follow-up time of 9.3 years (range 7.4-11.0 years).

RESULTS: Among 190,618 pregnant women, 1,252 were exposed to antidepressants during pregnancy. The average age at delivery was 31.2 years. 5,659 children who were born from these mothers were diagnosed with ADHD or received ADHD treatment. The crude hazard ratio (HR) of maternal antidepressant exposure during pregnancy was 2.28 (95% confidence interval [CI] 1.86-2.80, p-value<0.01) when compared to non-exposure. After adjustment for potential confounding factors, including maternal psychiatric disorders and use of other psychiatric medications, the adjusted HR was reduced to 1.40 (95%CI 1.11-1.78, p-value=0.01). Likewise, similar results were observed when comparing mothers who had antidepressant exposure before pregnancy and never users (adjusted HR=1.76, 95%CI 1.37-2.27, p-value<0.01). The risk of ADHD in the children of mothers with psychiatric disorders was higher even if the mothers had never used antidepressants (adjusted HR=1.83, 95%CI 1.54-2.18, p-value<0.01). A meta-analysis of the results obtained from previous research studies and the current study yielded similar results in all analyses.

CONCLUSIONS: We found that the risk of ADHD in children was elevated following use of antidepressants by the mother prior to conception, and when used during pregnancy but also in mothers with psychiatric illness without any psychotropic drugs exposure. Evidence from our study and meta-analysis indicates that the association between prenatal

antidepressant exposure and risk of ADHD is not causal but confounded by indication of antidepressants.

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder in children and adolescents.[1] It is characterised by pervasive hyperactivity, inattention and impulsiveness which impairs the lives of children.[1] ADHD is common among school-aged children with a worldwide prevalence of approximately 5-7%.[2, 3] Rates of diagnosis are high in North America and, whilst ADHD is under-diagnosed in most other parts of the world, rates of identified cases are increasing.[2] Due to its early onset, lifelong persistence and the high levels of associated comorbidities and impairment,[4] the negative impact of ADHD on social outcomes, education and health of patients and their caretakers is significant.[5] Understanding the risk factors for ADHD is an important public health task.

Recent studies have suggested a potential association between maternal prenatal exposure to antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs), and the risk of ADHD in children[6-10]. A systematic literature search identified five observational studies, including two cohort[6, 9] and three case-control studies,[7, 8, 10] which investigated the association between antidepressant use in pregnancy and ADHD in children. However, findings were inconsistent.[6-10] Two cohort studies started the follow-up on children at age zero and one year respectively whereas the two case-control studies restricted their study to children who were at least two years old.[6, 8-10] As ADHD is usually diagnosed from age five years onwards, previous studies may have identified an unrepresentative sample, leading to biased estimates of the actual risk. Furthermore, one of the most controversial issues for this association is whether the observed association between antidepressants in pregnancy and childhood ADHD is causal or may be confounded by other 'third factor' variables, such as underlying maternal psychiatric disorder (confounding by indication). ADHD is highly heritable and frequently co-morbid with other mental health problems including anxiety and depression, both of which are frequently treated with antidepressants.[11] The association between prenatal exposure to SSRI and ADHD could therefore be confounded by maternal/paternal psychiatric disorder.[7, 12] However, studies to date have not fully addressed this critical question. We hypothesised that the link between prenatal antidepressant exposure, including SSRIs, is not causal but rather is an indicator of maternal risk factors that are associated with an increased risk of ADHD in their offspring. Consequently, the aim of this study was to assess the association between maternal prenatal exposure to antidepressants and the risk of ADHD in their offspring and, in particular, to assess the possibility of

confounding by indication in this association by examining the effect of pre-existing maternal psychiatric illness.

Methods

Data source and study design:

A cohort study nested in the electronic health record from the Clinical Data Analysis and Reporting System (CDARS), a territory-wide database in Hong King (HK), was conducted. CDARS is a database developed by the Hong Kong Hospital Authority (HA), a statutory body that manages all public hospitals and their associated ambulatory clinics in HK. The HA health service is accessible to all HK residents (over 7 million). Data from CDARS has been used for various pharmacoepidemiological studies previously and has been found to be a reliable database for research.[13-19] The database contains patient-specific data, include demographic information, payment method, prescription information, pharmacy dispensing information, diagnosis, laboratory test results, admission and discharge information.[20] CDARS contains the records of all in-patient, out-patient and emergency room admissions in HA clinics and hospitals since 1995. Records are coded to protect patient confidentiality. A detailed description of CDARS can be found elsewhere.[16] This study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference number: UW 15-086).

Source population

The source population included all mothers who gave birth in public hospitals in HK between 1st January 2001 and 31st December 2009 so that by 31st December 2015, when our child outcome data were collected, all children would have at least 6 years' follow-up. Mothers without valid mother-child linkage and non-Hong Kong residents whose medical records are likely to be incomplete, were excluded. Only live births were included in the analysis. A valid linkage was defined as an exact match of mother and child patient identification numbers, delivery date and delivery hospital. The mother-child linkage is created by HA for clinical management, the mother and child records are linked permanently immediately after delivery; hence it is highly accurate.

Definition of pregnancy period

The gestation age of pregnancy is directly recorded by healthcare professionals and the last menstrual period (LMP) was calculated by date of delivery minus gestation age at

delivery. The pregnancy period was defined as the period between the LMP and the date of delivery with LMP as the start of cohort entry. Patient-time before the LMP was defined as pre-pregnancy. Patient-time was divided by the stage of pregnancy (first trimester (0-90 days after LMP), second trimester (91 to 180 days after LMP) and third trimester (181 days after LMP to delivery)) in order to examine any potential effects on the timing of exposure to antidepressants.

Exposure definition

Antidepressant exposure was extracted from the prescribing and dispensing records in CDARS. All drugs in the British National Formulary (BNF) chapter 4.3 were included. Exposure periods were defined as the length of time on medication and were estimated by the length of time between prescription start and end dates as recorded in CDARS for each prescription. Median treatment duration was used to impute data when prescription end dates were missing. The rate of missing data is low with 98.4% of antidepressant prescriptions having complete information in regard to treatment duration. A mother was considered exposed during the respective risk window if the medication exposure overlapped with a time point in that window. Based on the antidepressant exposure status in different risk periods, the cohort was classified into the following groups: (1) Never exposed before delivery (never users), (2) exposed before conception but stopped treatment when pregnant (pre-conception users), (3) non-gestation users are the combined group of never users and pre-conception users, and (4) exposed during pregnancy (gestation users).

Maternal psychiatric disorders diagnosed before and during pregnancy were also identified through CDARS. These were coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code 290-319. Patients were considered as having a psychiatric disorder(s) if the diagnosis date was recorded within a respective risk window.

Follow-up

The follow-up time of all live-born children started on the date of delivery/birth and ended at the date of ADHD diagnosis, date of first ADHD medication prescription or 31st December, 2015, whichever came first.

Outcome definition

Study outcomes in the live-born children were: an ADHD diagnosis, registered as ICD-9-CM diagnosis code 314, or a prescription of ADHD medication, namely methylphenidate or atomoxetine (BNF chapter 4.4), as recorded in CDARS as these are the only available medications in HK.

Covariates

Data on maternal comorbidities and other medications were obtained from CDARS. Covariates considered for confounding adjustment were maternal age at delivery, infant's gender, birth year, birth hospital, parity, maternal underlying illness before delivery (pre-existing diabetes, epilepsy, gestational diabetes, psychiatric conditions, hypertension; yes/no), other psychotropic medication use (antipsychotics, BNF chapter 4.2.1, 4.2.2), socioeconomic status.

Statistical Analysis

Several approaches were adopted in terms of the analysis. The first approach compared ADHD status in children between exposed (gestation users) and non-exposed (non-gestation users) mothers during pregnancy. Association between the exposure status for each trimester and outcome was evaluated using Cox proportional hazard regression models to estimate the hazard ratios. Covariates described above were selected and added to analytic models.

As mothers with severe psychiatric disorders may have a higher likelihood of being treated with antidepressants, three levels of adjustment were conducted to assess the effect of confounding by indication. The first model (model 1) included all the covariates mentioned above except maternal underlying psychiatric illness and other psychotropic medication use before delivery. Model 2 extended model 1 to include all maternal underlying psychiatric disorders. Model 3 added to model 2 by further adjusting for other concurrent psychotropic medication use. The analyses were repeated and antidepressants were split into subgroups (SSRI and non-SSRIs) to investigate class effects.

Another approach to the analyses was conducted by exploring the impact of confounding by indication. Firstly, we compared pre-conception users of antidepressant (who stopped their treatment before conception) to never users. We restricted the cohort to mothers who had no exposure to either antidepressants or antipsychotics during pregnancy. Mothers who had only used antidepressants before pregnancy were defined as the ‘pre-conception group’. An increased risk of ADHD in the offspring among the pre-conception group may

indicate confounding by indication of antidepressants as the foetus had no exposure to antidepressants. Secondly, the association between maternal psychiatric disorders and the risk of ADHD in children was assessed. The analysis was restricted to mothers with a psychiatric diagnosis who had never been exposed to antidepressants or antipsychotics before delivery (never users). This allowed us to estimate the role of maternal psychiatric disorder on ADHD in their offspring. Thirdly, we restricted the analysis to mothers who were exposed to either antidepressants or antipsychotics during pregnancy. We repeated the analyses by comparing the use of a) SSRIs vs non-SSRIs, b) antidepressants vs antipsychotics with the same method described above.

Several additional sensitivity analyses were conducted to test the validity and robustness of the study results. Firstly, a sensitivity analysis was conducted by including children who were born after 1st January 2009 to investigate the potential impact of under-diagnoses as the diagnosis rate has increased in recent years. Secondly, further analyses were conducted based on different drug non-adherence scenarios. Each exposed period was further extended by adding 30 and 60 days after the end of an exposed period to assess the effect of exposure misclassification. Thirdly children taking medications for ADHD but without an ADHD diagnosis were removed from the analysis.

A significance level of 5% was used in all statistical analyses. Microsoft Excel® and Statistical Analysis System® (SAS) v9.3 (SAS Institute Inc, Cary, North Carolina, United States) were used for data manipulation and analysis. KM and WL conducted the analyses independently. The programming and results were cross-checked for accuracy and consistency.

Systematic review and meta-analysis

A meta-analysis of the study results together with data from previous research studies was conducted. Three pooled estimates of ADHD risk in children were evaluated from the meta-analysis: 1) antidepressant use in pregnancy (user vs non-user), 2) antidepressant use before pregnancy (previous user vs non-user), 3) psychiatric disorders in mothers during pregnancy (yes vs no). Both the crude and the fully adjusted rate ratios (RRs) were pooled in the meta-analysis. Details of the search terms and analyses are included in supplementary material 1.

Patient involvement

Patients were not involved in the development of plans for recruitment, design and implementation of the study.

Results

190,618 pairs of mother-child records were included in the analysis (Figure 1). The mean maternal age at delivery was 31.2 years with a standard deviation of 5.1 years (Table 1). 1,252 mothers were exposed to antidepressants during pregnancy. Among them, 425 and 470 received SSRI and non-SSRI antidepressant monotherapy respectively; 129 had both SSRI and non-SSRI treatment, 101 received SSRI and antipsychotics, 91 received non-SSRI and antipsychotics and 36 received SSRI, non-SSRI and antipsychotics. 2,275 mothers received antidepressants prior to pregnancy; 1,486 had discontinued antidepressants before pregnancy started and 789 continued their treatment into pregnancy (Tables 2 and 3).

In this cohort, 5,659 children were diagnosed with ADHD or received an ADHD medication. The mean follow-up time was 9.28 years (range 7.4-11.0 years). The crude hazard ratio (HR) of antidepressant exposure during pregnancy and ADHD was 2.28 (95% confidence interval [CI] 1.86-2.80) when comparing gestation user to non-user. The estimate was similar in model 1 (adjusted HR=2.40, 95%CI 1.95-2.95) but reduced to 1.40 (95%CI 1.11-1.77) and 1.40 (95%CI 1.11-1.78) in models 2 and 3 respectively, when maternal psychiatric disorder and additionally other psychotropic medications were included. The corresponding HRs in different trimesters were similar. The fully adjusted HRs (model 3) were 1.44 (95%CI 1.06-1.96), 1.51 (95%CI 1.09-2.10) and 1.43 (95%CI 1.04-1.96) for 1st to 3rd trimester respectively.

Results were slightly different when antidepressants were broken down into SSRIs and non-SSRIs. The HRs for SSRIs and non-SSRIs were similar in the crude estimate and model 1 but different in models 2 and 3. In model 3, the adjusted HR for SSRIs was 1.12 (95%CI 0.78-1.60) whereas for non-SSRIs the HR was 1.59 (95%CI 1.18-2.15). The results are summarised in Table 4.

Comparison of pre-conception users to never users

When comparing pre-conception users of antidepressants to never users, the crude HR was 2.91 (95%CI 2.36-3.60) and the adjusted HR was 1.76 (95%CI 1.37-2.27) in model 3. The risk of ADHD in children was significantly increased in pre-conception users (Table 5).

Comparison of never user mothers with psychiatric disorders to never user mothers without psychiatric disorders

When the analysis was restricted to mothers who had never been exposed to either antidepressants or antipsychotics, the risk of ADHD in children was higher in mothers with psychiatric disorders. The fully adjusted HR for psychiatric disorders before pregnancy was 1.95 (95%CI 1.62-2.33) and 1.83 (95%CI 1.54-2.18) during pregnancy. The risk estimates were similar to those for both pre-conception users and current users (Table 5).

Comparison of prenatal exposure to antidepressants with antipsychotics

Prenatal exposure to antidepressants had a crude HR of 1.15 (95%CI 0.70-1.90) for risk of ADHD compared to prenatal exposure to antipsychotics and a fully adjusted HR of 1.28 (95%CI 0.76-2.16). The comparison between exposure to SSRI and non-SSRI antidepressants showed no significant difference between the two drug classes with a crude HR of 0.75 (95%CI 0.44-1.28) for the risk of ADHD and fully adjusted HR of 0.70 (95%CI 0.40-1.24) (Table 5).

Sensitivity analyses

All other sensitivity analyses returned similar results as the main analyses (Supplementary material 6 to 8).

Systematic review and meta-analysis

The systematic review returned five observational studies[6-8, 10], one[9] was obtained from another source (Supplementary material 2). Two studies utilised the same data source with different matching strategies[8, 10] and therefore Clements et al.[10] was included in the primary meta-analysis and was substituted by Castro et al.[8] in subsequent sensitivity analysis. A summary of the included studies and quality assessment were in supplementary material 3 to 5.

The pooled estimates comparing gestational users to non-users showed crude and adjusted RRs of 2.21 (95%CI 1.99-2.46) and 1.39 (95%CI 1.17-1.66), respectively. Similar results were found comparing previous users and non-users: crude RR=2.17 (95%CI 1.51-3.10), adjusted RR=1.54 (95%CI 1.22-1.95). Maternal psychiatric conditions during pregnancy yielded a pooled crude RR of 2.62 (95%CI 1.91-3.60) and adjusted RR of 2.07 (95%CI 1.73-2.48) (Figure 2-4, supplementary material 9-11). No material difference was found when Clements et al.[10] was replaced with Castro et al.[8] in all analyses (Supplementary material 12-17).

Discussion

This cohort study of over 190,000 mother-child pairs in the Hong Kong CDARS, found that prenatal antidepressant exposure is associated with an increased risk of ADHD. However the risk of ADHD was similarly increased for pre-conception use of antidepressants and in children of mothers with psychiatric disorders who had not been treated.

Most of the published studies, with the exception of Castro et al.,[8] reported similar results with the risk of prenatal exposure to antidepressants and ADHD ranging from 1.16 to 1.81.[6, 8-10, 21]. There is no biological explanation regard to pre-conception exposure to antidepressants and ADHD in offspring. Based on the effect of psychiatric disease on ADHD and pre-conception exposure, it is likely that the increased risk for prenatal exposure may at least be partially explained by confounding due to pre-existing conditions. ADHD is highly heritable[22, 23] and parents of children with ADHD are themselves more likely to suffer the same or related mental disorders. In recent years, it has become apparent that whilst ADHD often persists into adulthood, and is associated with high levels of psychiatric comorbidity, including increased rates of depression and anxiety, many adults with ADHD are never properly diagnosed or treated.[24] This may explain why we found a possible link between psychiatric disorders in mothers and ADHD in children. Consequently, the findings support the argument that the association between antidepressant use in pregnancy and ADHD is likely confounded by psychiatric disorders. Indeed this study has also found that mothers with maternal psychiatric disorders without pharmacological treatment are at similar increased risk of having off-spring with ADHD.

The results of the meta-analysis were similar to the estimates from the cohort study when comparing gestation exposed mother to non-gestation exposed mothers. Similarly, the risk of ADHD in children was higher in those born to mothers with maternal psychiatric disorders even without pharmacological treatment. We believe that the current evidence supports that the association is not causal but confounded by indication of antidepressants.

Several important limitations need to be addressed. CDARS only contains information from publicly funded healthcare medical records and therefore does not include data from private medical practitioners/hospitals. Based on the birth statistics in HK, there were about 45,000 live births to local mothers in 2009.[25] Our data captured over 31,000 birth episodes in the same year thus including about 70% of births in HK.[25] Notably, the public sector is the main provider of specialist care for neurodevelopmental disorders in HK.[26] Children with neurodevelopmental disorders usually require comprehensive long-term

treatment and monitoring, hence they are usually under the care of publicly funded healthcare. Therefore, it is likely that the vast majority of children who received a diagnosis of ADHD will have been included in this study.

As exposure is defined by prescriptions written by clinicians and dispensed by pharmacy, it is unclear whether the actual medications were actually taken by individuals in accordance with information on the prescription (adherence) ie exposure to drugs might have lasted longer than the intended prescribing period. We addressed exposure misclassification by conducting a duration-outcome analysis by adding 30 and 60 days after the end of an exposed period.

Since the first report of a possible association between antidepressant exposure in utero and childhood neurodevelopmental disorders, both patients and clinicians have faced a dilemma regarding the management of women who are experiencing severe affective disorders both at the time that they are trying to conceive and during pregnancy. There can be significant adverse effects in terms of stopping medication abruptly or withholding antidepressant medication during pregnancy. The present findings provide useful data to help guide clinical decision-making.

In conclusion, in this population based study with territory-wide electronic health record data 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, preconception users (i.e. who stopped their treatment before pregnancy), as well mothers who were never treated but who had psychiatric disorder showed similar results. Therefore, it cannot be concluded that antidepressant use in pregnancy is causally associated with an increased risk of ADHD in children. These results support the hypothesis that the association of ADHD in offspring with maternal prenatal antidepressant exposure is likely to be confounded by maternal underlying psychiatric disorders. However, decision making about antidepressant use in pregnancy remains important and requires an assessment of the risks and benefits in the context of the individual patient and family.

What is already known on this topic:

- **The use of pharmacological treatment for depression during pregnancy is a complex clinical decision.**
- **Prenatal exposure to antidepressants is considered a risk factor for attention deficit hyperactivity disorder (ADHD) in children but existing evidence is inconclusive.**
- **The negative consequences of untreated maternal depression might also affect childhood development.**

What this study adds:

- **Gestation mothers exposed to antidepressant medication have a similar risk as non-gestation exposed mothers in terms of their child having ADHD.**
- **The risk of ADHD in children was higher for those born to mothers with maternal psychiatric disorders even without pharmacological treatment.**
- **Current evidence suggests that the association between prenatal antidepressant exposure and risk of ADHD is not causal but confounded by indication of antidepressants.**

Footnotes

Contributors: KM and IW had the original idea for this study, contributed to the development of the study, extracted data from the source database, constructed the study design and the statistical model, reviewed the literature, KM and WL undertook the statistical analysis, KM wrote the first draft of the manuscript. PI and PC validated the diagnosis codes from the database. IW is the principal investigator and provided oversight for all aspects of this project. MCJMS and MS provided critical input to the analyses and design. All authors contributed to the interpretation of the analysis, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

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Transparency declaration: The corresponding author (ICKW) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethical approval: This study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference Number: UW15-086).

Data sharing: No additional data available.

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Table 1: Patient characteristics in mothers and children (by gestation exposure)

	SSRI[a] only	Other antidepressants only	Antipsychotics only	SSRI and other antidepressants	SSRI and antipsychotics	Other antidepressants and antipsychotics	All	Unexposed
	(n=425)	(n=470)	(n=364)	(n=129)	(n=101)	(n=91)	(n=36)	(n=189,002)
In mothers								
Maternal Delivery Age in years	32.0	32.7	31.7	32.0	32.0	33.0	31.5	31.2
(S.D.)	5.71	5.28	5.60	5.73	5.89	5.68	7.26	5.10
Maternal underlying diseases (%)								
Epilepsy	1 (0.2)	3 (0.6)	1 (0.3)	1 (0.8)	0 (0.0)	1 (1.1)	1 (2.8)	299 (0.16)
Diabetes mellitus before pregnancy	1 (0.2)	7 (1.5)	2 (0.6)	1 (0.8)	0 (0.0)	2 (2.2)	1 (2.8)	444 (0.2)
Gestational diabetes mellitus	14 (3.3)	27 (5.7)	26 (7.1)	4 (3.1)	9 (8.9)	6 (6.5)	1 (2.8)	5,112 (2.7)
Hypertension	13 (3)	24 (5.1)	17 (4.7)	1 (0.8)	2 (2.0)	7 (7.5)	2 (5.6)	6,393 (3.4)
Psychiatric illness	295 (69.4)	315 (67.0)	308 (84.6)	103 (79.8)	84 (83.2)	72 (77.4)	31 (86.1)	2,978 (1.6)

Parity (%)								
0	138 (32.5)	152 (32.4)	183 (50.3)	38 (29.5)	41 (40.6)	36 (38.7)	15 (41.7)	97,599 (51.6)
1	172 (40.5)	205 (43.6)	102 (28.0)	48 (37.2)	32 (31.7)	35 (37.6)	11 (30.6)	70,962 (37.6)
2	78 (18.4)	69 (14.7)	51 (14.0)	35 (27.1)	22 (21.8)	15 (16.1)	5 (16.7)	16,023 (8.5)
3+	37 (8.7)	44 (9.4)	28 (7.7)	8 (6.2)	6 (5.9)	7 (7.5)	4 (11.1)	4,418 (2.3)
Median household income (%)								
< HKD19,300	75 (17.7)	106 (22.6)	93 (25.6)	18 (14.0)	18 (17.8)	13 (14.0)	8 (22.2)	37,828 (20.0)
HKD19,300-21,999	137 (32.2)	192 (40.9)	117 (32.1)	47 (36.4)	42 (41.6)	34 (36.6)	11 (30.6)	54,675 (28.9)
HKD22,000-25,999	107 (25.2)	79 (16.8)	88 (24.2)	40 (31.0)	22 (21.8)	23 (24.7)	11 (30.6)	46,018 (24.4)
HKD26,000+	106 (24.9)	93 (19.8)	66 (18.1)	24 (18.6)	19 (18.8)	23 (24.7)	6 (16.7)	50,481 (26.7)
In children								
Average follow-up time (patient-year)	8.4	9.3	9.5	8.8	8.7	9.7	8.1	9.3

ADHD (%)	18 (4.2)	31 (6.6)	21 (5.8)	9 (7.0)	3 (3.0)	8 (8.6)	5 (13.9)	5,564 (2.9)
Infant's gender (male, %)	239 (56.2)	248 (52.8)	192 (52.8)	65 (50.4)	56 (55.5)	50 (53.8)	17 (47.2)	98,316 (52.0)
Delivery method (Normal Spontaneous Delivery, %)	288 (67.8)	300 (63.8)	233 (64.0)	82 (63.6)	65 (64.3)	54 (58.1)	31 (86.1)	123,834 (65.5)
Multiple pregnancy (Y/N, %)	6 (1.4)	12 (2.6)	4 (1.1)	4 (3.1)	4 (4.0)	0 (0.0)	0 (0.0)	5,466 (2.9)
Birth trauma (Y/N, %)	1 (0.2)	3 (0.6)	1 (0.3)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	862 (0.5)
Apgar score at 1-minute < 7 (%)	16 (3.8)	20 (4.3)	22 (6.0)	8 (6.2)	11 (10.9)	6 (6.5)	5 (13.9)	6,983 (3.7)
Apgar score at 5-minute < 7 (%)	0 (0.0)	1 (0.2)	1 (0.3)	2 (1.6)	2 (2.0)	1 (1.1)	0 (0.0)	591 (0.3)
Birth weight (%)								
< 1500 gram	6 (1.4)	5 (1.1)	7 (1.9)	2 (1.6)	3 (3.0)	1 (1.1)	0 (0.0)	2,213 (1.2)
1500-2499 gram	33 (7.8)	50 (10.6)	28 (7.7)	9 (7.0)	11 (10.9)	10 (10.8)	5 (13.9)	14,291 (7.6)

2500+ gram	386 (90.8)	415 (88.3)	329 (90.4)	118 (91.5)	87 (86.1)	82 (88.2)	31 (86.1)	172,498 (91.3)
Gestation weeks (%)								
<32	7 (1.7)	7 (1.5)	12 (3.3)	3 (2.3)	2 (2.0)	3 (3.2)	0 (0.0)	3,502 (1.9)
33-36	34 (8)	54 (11.5)	32 (8.8)	7 (5.4)	12 (11.9)	14 (15.1)	5 (13.9)	12,753 (6.8)
>36	384 (90.3)	409 (87.0)	320 (87.9)	119 (92.3)	87 (86.1)	76 (81.7)	31 (86.1)	172,747 (91.3)

[a]SSRI=Selective serotonin re-uptake inhibitor

Table 2: Treatment utilisation of antidepressants and antipsychotics in the cohort

Period	SSRI[a] only	Other antidepressant only	Antipsychotic only	SSRI and other antidepressant	SSRI and antipsychotic	Other antidepressant and antipsychotic	All[b]	Non-exposed
Before Pregnancy	553	849	475	360	171	155	187	187,868
During Pregnancy	425	470	364	129	101	91	36	189,002
1st Trimester	324	294	298	58	86	69	14	189,475
2nd Trimester	235	273	280	49	55	59	13	189,654
3rd Trimester	250	320	298	38	56	56	8	189,592

[a]SSRI= Selective serotonin re-uptake inhibitor.

[b]Patients exposed to SSRI, other antidepressants and antipsychotics in that period.

Table 3: Treatment continuation and switching pattern in the cohort

During pregnancy	SSRI only	Other antidepressant only	Antipsychotic only	SSRI and other antidepressant	SSRI and antipsychotic	Other antidepressant and antipsychotic	All
Discontinued[a]	367	667	234	185	77	76	58
Continued[b]	144	156	231	42	42	32	13
New user	155	217	77	38	19	17	7
Switched to other regimen	42	26	10	133	52	47	116
Switched from other regimen	126	97	56	49	40	42	16

[a]Patients who were on that treatment regimen before pregnancy and stopped before pregnancy started.

[b]Patients who were on that treatment regimen before pregnancy and continued when pregnancy started.

Table 4: Results from the analysis comparing gestation user vs non-gestation user

Exposure	Crude estimate			Model 1[a]			Model 2[b]			Model 3[c]		
	HR[d]	95%CI[e]	p-value	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Antidepressants												
During Pregnancy	2.28	1.86 2.80	<0.01	2.40	1.95 2.95	<0.01	1.40	1.11 1.77	<0.01	1.40	1.11 1.78	<0.01
1st Trimester	2.30	1.74 3.03	<0.01	2.46	1.86 3.25	<0.01	1.49	1.10 2.00	<0.01	1.44	1.06 1.96	0.02
2nd Trimester	2.41	1.78 3.25	<0.01	2.66	1.97 3.59	<0.01	1.52	1.10 2.10	0.01	1.51	1.09 2.10	0.01
3rd Trimester	2.35	1.75 3.15	<0.01	2.53	1.89 3.40	<0.01	1.39	1.01 1.91	0.04	1.43	1.04 1.96	0.03
SSRIs												
During Pregnancy	2.16	1.55 3.01	<0.01	2.23	1.60 3.11	<0.01	1.23	0.87 1.75	0.24	1.12	0.78 1.60	0.55
1st Trimester	2.20	1.49 3.26	<0.01	2.33	1.57 3.45	<0.01	1.31	0.87 1.97	0.19	1.19	0.78 1.80	0.42
2nd Trimester	2.11	1.31 3.40	<0.01	2.23	1.38 3.58	<0.01	1.20	0.74 1.96	0.46	1.11	0.67 1.81	0.69
3rd Trimester	2.20	1.39 3.49	<0.01	2.26	1.42 3.59	<0.01	1.19	0.74 1.92	0.48	1.16	0.72 1.87	0.55
Non-SSRIs												
During Pregnancy	2.55	1.94 3.34	<0.01	2.75	2.10 3.61	<0.01	1.63	1.22 2.19	<0.01	1.59	1.18 2.15	<0.01
1st Trimester	2.57	1.82 3.64	<0.01	2.81	1.98 3.98	<0.01	1.74	1.21 2.50	<0.01	1.65	1.14 2.40	<0.01
2nd	2.69	1.88 3.85	<0.01	3.05	2.13 4.37	<0.01	1.76	1.21 2.56	<0.01	1.73	1.18 2.53	<0.01

Trimester																
3rd Trimester	2.68	1.89	3.79	<0.01	2.94	2.08	4.17	<0.01	1.62	1.12	2.33	0.01	1.65	1.14	2.38	<0.01

[a]Model 1 adjusted maternal age at delivery, infant's gender, birth year, birth hospital, parity, maternal underlying illness before delivery (pre-existing diabetes, epilepsy, gestational diabetes, hypertension; yes/no) and socioeconomic status.

[b]Model 2 adjusted all the factors in model 1 and maternal psychiatric conditions.

[c]Model 3 adjusted all the factors in model 2 and other psychiatric medication use.

[d]HR=Hazard ratio

[e]CI=Confidence interval

Table 5: Results from analyses of different comparisons

Exposure	Crude estimate			Model 1[a]			Model 2[b]			Model 3[c]		
	HR[d]	95%CI[e]	p-value	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Antidepressants (pre-conception user vs never user)												
Before Pregnancy	2.91	2.36 3.60	<0.01	2.75	2.22 3.39	<0.01	1.77	1.39 2.26	<0.01	1.76	1.37 2.27	<0.01
SSRIs (pre-conception user vs never user)												
Before Pregnancy	2.91	2.12 3.98	<0.01	2.65	1.93 3.63	<0.01	1.43	1.01 2.01	0.04	1.20	0.84 1.71	0.32
Non-SSRIs (pre-conception user vs never user)												
Before Pregnancy	3.11	2.44 3.97	<0.01	2.94	2.31 3.75	<0.01	1.91	1.46 2.50	<0.01	1.83	1.39 2.43	<0.01
Mother Psychiatric disorder in never users[f]												
Before Pregnancy	2.03	1.69 2.43	<0.01	1.95	1.62 2.33	<0.01	--	-- --	--	--	-- --	--
During Pregnancy	1.96	1.65 2.32	<0.01	1.83	1.54 2.18	<0.01	--	-- --	--	--	-- --	--
Gestation SSRI user vs Gestation Non-SSRI antidepressant user												
Before Pregnancy	0.83	0.50 1.37	0.47	0.84	0.49 1.43	0.51	0.82	0.48 1.42	0.48	0.82	0.47 1.42	0.48
During Pregnancy	0.75	0.44 1.28	0.30	0.73	0.42 1.29	0.28	0.70	0.40 1.24	0.22	0.70	0.40 1.24	0.22
Gestation Antidepressants user vs Gestation Antipsychotics user												
Before Pregnancy	1.25	0.71 2.21	0.44	1.47	0.81 2.65	0.20	1.49	0.83 2.70	0.19	--	-- --	--
During Pregnancy	1.15	0.70 1.90	0.58	1.20	0.71 2.02	0.49	1.28	0.76 2.16	0.36	--	-- --	--

[a]Model 1 adjusted maternal age at delivery, infant's gender, birth year, birth hospital, parity, maternal underlying illness before delivery (pre-existing diabetes, epilepsy, gestational diabetes, hypertension; yes/no) and socioeconomic status.
[b]Model 2 adjusted all the factors in model 1 and maternal psychiatric conditions.
[c]Model 3 adjusted all the factors in model 2 and other psychiatric medication use.
[d]HR=Hazard ratio
[e]CI=Confidence interval
[f]Identified by International Classification to Disease, Ninth Revision, Clinical Modification diagnosis code 290-319, defined as Yes vs No

Figure 1: Flowchart of mother-child pairs identification

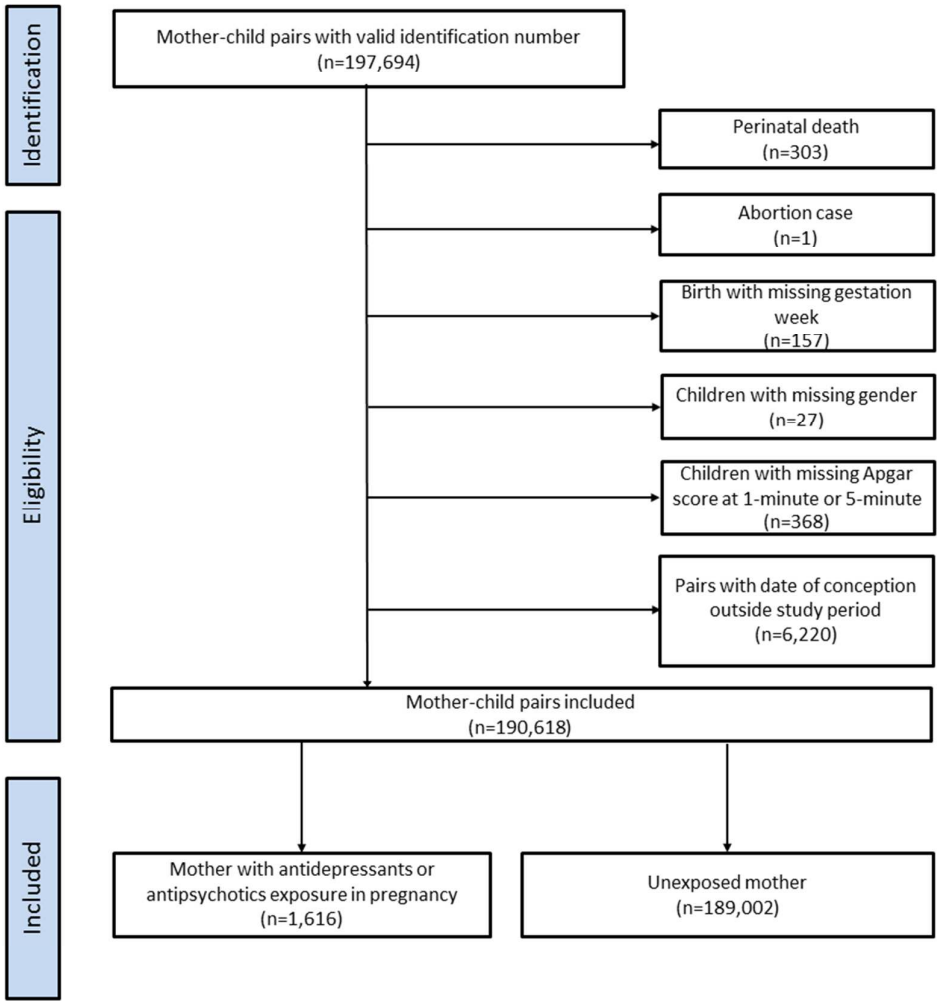


Figure 2: Antidepressants user vs non-user (adjusted estimate)

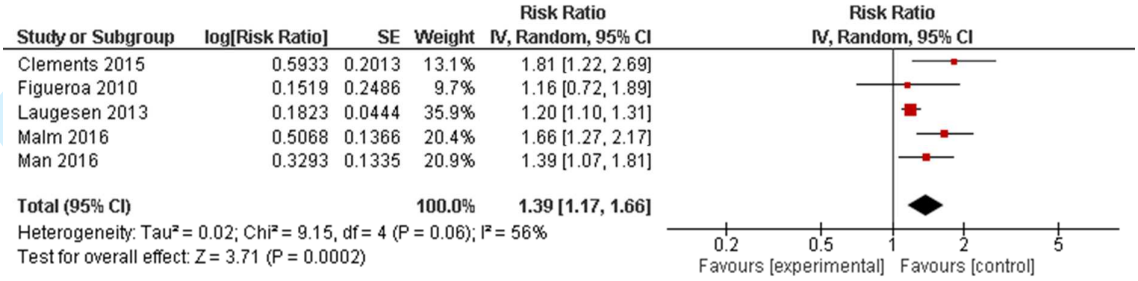


Figure 3: Previous antidepressants user vs non-user (adjusted estimate)

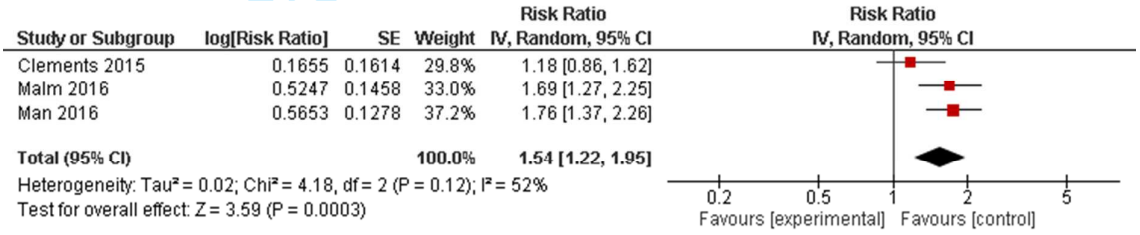
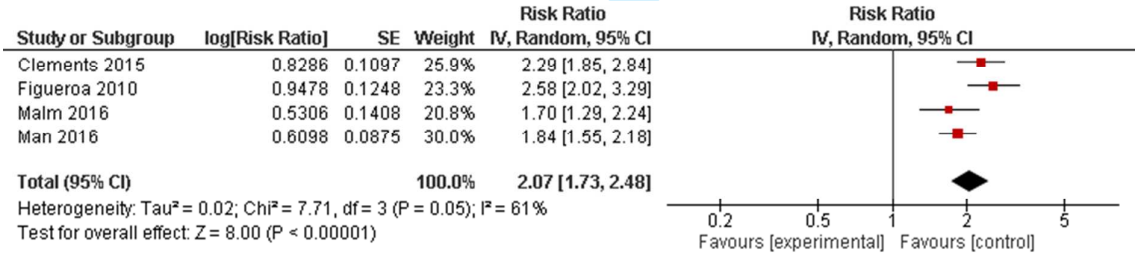


Figure 4: Maternal psychiatric conditions (adjusted estimate)



Appendix: Prenatal antidepressant exposure and the risk of attention-deficit hyperactivity disorder: A population based cohort study and meta-analysis

Contents

Supplementary material 1: Systematic review and meta-analysis method

The systematic literature search was conducted using the following search terms: (Depressive disorder/drug therapy OR antidepressive agent* OR antidepressant* OR Selective serotonin reuptake inhibitor* OR SSRI* OR serotonin uptake inhibitor* OR serotonin OR fluoxetine OR citalopram OR paroxetine OR sertraline OR fluvoxamine OR escitalopram OR vortioxetine OR
Serotonin norepinephrine reuptake inhibitor* OR SNRI* OR duloxetine OR levomilnacipran OR venlafaxine OR desvenlafaxine OR milnacipran OR Tricyclic antidepressant* OR TCA* OR amitriptyline OR doxepin OR imipramine OR Trimipramine OR nortriptyline OR amoxapine OR desipramine OR protriptyline
OR clomipramine OR dosulepin OR lofepramine OR Monoamine oxidase inhibitor* OR MAOI* OR MAO inhibitor* OR isocarboxazid
OR phenelzine OR selegiline OR tranylcypromine OR moclobemide OR Trazodone OR nefazodone OR mirtazapine OR bupropion
OR vilazodone OR agomelatine OR mianserin OR reboxetine OR flupentixol OR maprotiline)
AND (pregnant women OR pregnant woman OR pregnan* OR pregnancy complications/drug therapy)
AND (ADHD* OR attention deficit* OR hyperactivity disorder* OR attention deficit hyperactivity disorder* OR hyperkinetic* OR hyperactiv* OR inattent* OR impulsi*).

PubMed, EMBASE and PsycINFO were searched up to 12 April, 2016. Observational studies, including cohort and case-control study designs, which investigated the association between antidepressant use in pregnancy and ADHD in children were included. 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 further identify pertinent studies.

Quality assessment

As recommended by the Cochrane Collaboration[1], the methodological quality of the included studies were assessed using the Newcastle-Ottawa Scale (NOS)[2]. 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.

Statistical analysis

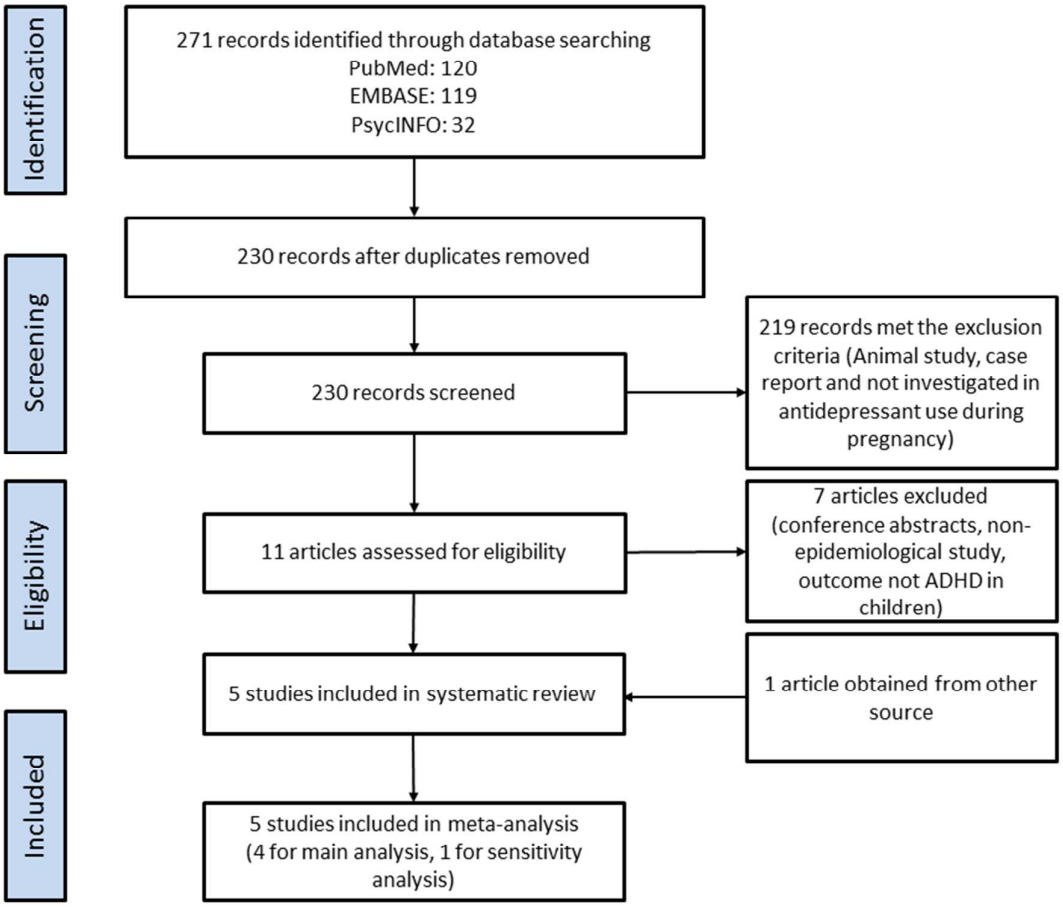
Three pooled estimates of ADHD risk in children were evaluated from the meta-analysis: 1) Antidepressants use in pregnancy (user vs non-user), 2) Antidepressants use before pregnancy (previous user vs non-user), 3) Psychiatric conditions in mothers during pregnancy (yes vs no). Both the crude and the fully adjusted rate ratios (RRs) were pooled in the meta-analysis. 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[1],

where a cut-off p-value of 0.1 was considered significant for heterogeneity. Higgin's I^2-statistic[1] was reported for each figure. The pooled estimates were estimated using DerSimonian and Laird's random-effects model[3] 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. Two included studies, Castro et al. (2016) and Clements et al. (2015) were utilising the same data source. Therefore, sensitivity analysis was performed by substituting the findings of Clements et al. with those of Castro et al. 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).

References:

1. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. 2011. www.cochrane-handbook.org (accessed 4 Aug 2014.
2. Wells G, Shea B, O'connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Resoruce document. Ottawa Hospital Research Institute. ; 2000.
3. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7(3): 177-88.

Supplementary material 2: Flowchart for studies inclusion



Abbreviations: ADHD=Attention deficit hyperactivity disorder.

Supplementary material 3: Summary of included studies

Study	Data Source	Study period	Country	Inclusion criteria	Exclusion criteria	Control definition	Exposure duration definition
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. 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.	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 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.	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.
Clements 2015	Three independent electronic health records: the Partners HealthCare system, which spans Massachusetts General	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	If mother -child matches could not be confirmed, those pairs were omitted from analysis. Restricted	Children were then matched 1:3 with healthy control children delivered at MGH, Brigham and Women's	Exposures were identified using e-prescribing data in the EHR, both

	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 Registry of Vital Records and Statistics.			1997 and 2010, delivered at MGH, Brigham and Women's Hospital, Newton-Wellesley Hospital or BIDMC.	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.	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 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.	inpatient and outpatient, which record number of pills, frequency and refill number, allowing calculation of exposure period.
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	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

				codes 370 to 375			(tricyclics, tetracyclics, mirtazapine, and venlafaxine).
Laugesen 2013	Danish Medical Birth Registry; Danish National Prescription Registry; Danish Psychiatric Central Register; Danish Civil Registration System; Danish National Hospital Register	1996-2009	Danish	All singletons born alive from 1996 until the end of 2009. ADHD was detected either as a diagnosis of ADHD or redemption of a prescription for ADHD medication	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 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

Supplementary material 4: Quality assessment by Newcastle-Ottawa Scale

Study	study design	selection	comparability	exposure/outcome	total
Castro 2016	Case-control	***	**	***	8
Clements 2015	Case-control	***	**	***	8
Figueroa 2010	Case-control	****	**	**	8
Laugesen 2013	Cohort	****	**	**	8
Malm 2016	Cohort	****	**	**	8

Supplementary material 5: 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
Castro 2016	5498	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	7874	ADHD group: 63 with antidepressant; 2175 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	38074	ADHD group: 23 with SSRI, 5 with Bupropion, 1 with other antidepressant; Control group: 893 with SSRI, 109 with Bupropion, 118 with other antidepressant;	2.32[e] (95% CI 1.59-3.38)	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	877778	Antidepressants group: 432[e] with ADHD, 14576[e] without ADHD Unexposed group: 12409[e] with ADHD, 850361[e] without ADHD	2.00 (95% CI 1.70-2.30)	Gender of the child, calendar time at birth, birth order, maternal age at birth, maternal smoking status, maternal psychiatric diagnoses, paternal psychiatric diagnoses, maternal diseases during pregnancy (infections, epilepsy) and maternal anxiolytics/hypnotics/sedatives use during pregnancy	1.20 (95% CI 1.10-1.40)
Malm 2016	47123	SSRIs group: 160 with ADHD; 15569 without ADHD	2.62	Sex; socioeconomic status; smoking during pregnancy; neonatal care unit; maternal history of other psychiatric diagnosis; maternal history of substance	1.66

		Unexposed group: 124 with ASD; 31270 without ASD	(95% CI 2.06-3.34)	abuse; paternal history of psychiatric diagnosis; parental death	(95% CI 1.27-2.16)

[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

Supplementary material 6: Sensitivity analysis of including children born after 2009

Exposure	Crude estimate				Model 1				Model 2				Model 3			
	HR	95%CI		p-value	HR	95%CI		p-value	HR	95%CI		p-value	HR	95%CI		p-value
Antidepressants (Included children born after 2009)																
During Pregnancy	2.31	1.91	2.80	<0.01	2.43	2.01	2.94	<0.01	1.44	1.16	1.79	<0.01	1.44	1.16	1.80	<0.01
1st Trimester	2.39	1.92	2.99	<0.01	2.52	2.02	3.15	<0.01	1.54	1.21	1.96	<0.01	1.51	1.18	1.94	<0.01
2nd Trimester	2.34	1.87	2.94	<0.01	2.48	1.97	3.11	<0.01	1.43	1.12	1.84	<0.01	1.41	1.09	1.82	<0.01
3rd Trimester	2.23	1.77	2.80	<0.01	2.36	1.87	2.98	<0.01	1.29	1.00	1.67	0.05	1.32	1.02	1.71	0.03
SSRIs (Included children born after 2009)																
During Pregnancy	2.01	1.51	2.67	<0.01	2.05	1.55	2.73	<0.01	1.13	0.84	1.53	0.43	1.00	0.73	1.36	1.00
1st Trimester	2.10	1.52	2.88	<0.01	2.16	1.57	2.98	<0.01	1.23	0.88	1.72	0.22	1.07	0.76	1.50	0.71
2nd Trimester	2.12	1.52	2.96	<0.01	2.21	1.58	3.08	<0.01	1.19	0.84	1.69	0.32	1.07	0.75	1.53	0.71
3rd Trimester	2.04	1.44	2.91	<0.01	2.09	1.47	2.98	<0.01	1.09	0.76	1.58	0.64	1.05	0.72	1.52	0.81
Non-SSRIs (Included children born after 2009)																
During Pregnancy	2.69	2.15	3.36	<0.01	2.88	2.30	3.60	<0.01	1.72	1.34	2.19	<0.01	1.72	1.33	2.21	<0.01
1st Trimester	2.90	2.23	3.77	<0.01	3.11	2.39	4.05	<0.01	1.93	1.46	2.56	<0.01	1.88	1.41	2.52	<0.01
2nd Trimester	2.59	1.97	3.40	<0.01	2.53	2.11	3.64	<0.01	1.61	1.21	2.16	<0.01	1.57	1.16	2.12	<0.01
3rd Trimester	2.55	1.94	3.34	<0.01	2.76	2.11	3.62	<0.01	1.52	1.14	2.04	<0.01	1.56	1.16	2.09	<0.01

Supplementary material 7: Sensitivity analysis of extending exposure period

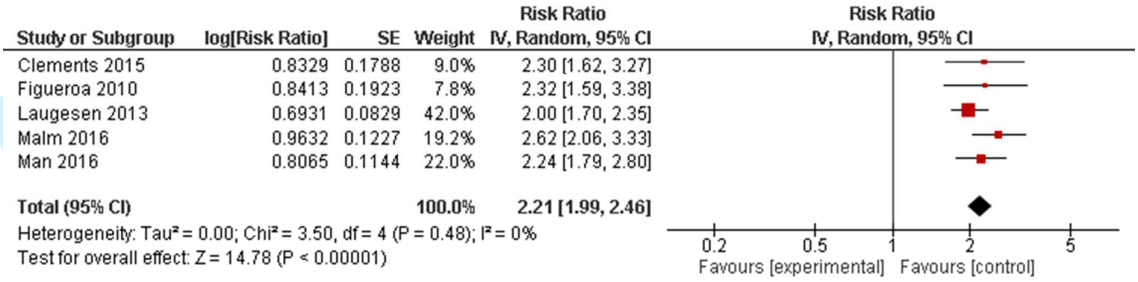
Exposure	Crude estimate				Model 1				Model 2				Model 3			
	HR	95%CI		p-value	HR	95%CI		p-value	HR	95%CI		p-value	HR	95%CI		p-value
Antidepressants (exposure extended by 30 days)																
During Pregnancy	2.35	1.92	2.86	<0.01	2.48	2.03	3.02	<0.01	1.48	1.18	1.86	<0.01	1.49	1.18	1.84	<0.01
1st Trimester	2.45	1.95	3.10	<0.01	2.60	2.06	3.29	<0.01	1.59	1.24	2.05	<0.01	1.57	1.21	2.04	<0.01
2nd Trimester	2.60	2.05	3.28	<0.01	2.76	2.19	3.50	<0.01	1.62	1.25	2.10	<0.01	1.63	1.25	2.12	<0.01
3rd Trimester	2.28	1.76	2.95	<0.01	2.44	1.89	3.15	<0.01	1.34	1.01	1.77	0.04	1.38	1.04	1.83	0.02
SSRIs (exposure extended by 30 days)																
During Pregnancy	2.18	1.63	2.91	<0.01	2.26	1.69	3.03	<0.01	1.26	0.92	1.71	0.15	1.13	0.83	1.55	0.44
1st Trimester	2.19	1.57	3.07	<0.01	2.31	1.65	3.24	<0.01	1.31	0.92	1.86	0.13	1.17	0.82	1.68	0.38
2nd Trimester	2.44	1.74	3.44	<0.01	2.52	1.79	3.54	<0.01	1.36	0.95	1.95	0.09	1.22	0.84	1.76	0.29
3rd Trimester	2.00	1.32	3.05	<0.01	2.09	1.38	3.18	<0.01	1.10	0.72	1.70	0.66	1.07	0.69	1.65	0.76
Non-SSRIs (exposure extended by 30 days)																
During Pregnancy	2.69	2.31	3.39	<0.01	2.86	2.26	3.61	<0.01	1.71	1.32	2.21	<0.01	1.68	1.30	2.19	<0.01
1st Trimester	2.94	2.22	3.90	<0.01	3.14	2.37	4.16	<0.01	1.96	1.46	2.63	<0.01	1.89	1.39	2.58	<0.01
2nd Trimester	2.84	2.14	3.78	<0.01	3.06	2.30	4.08	<0.01	1.80	1.33	2.43	<0.01	1.75	1.28	2.39	<0.01
3rd Trimester	2.74	2.04	3.67	<0.01	2.93	2.18	3.93	<0.01	1.62	1.19	2.22	<0.01	1.67	1.22	2.29	<0.01
Antidepressants (exposure extended by 60 days)																
During Pregnancy	2.37	1.95	2.87	<0.01	2.49	2.05	3.01	<0.01	1.52	1.22	1.89	<0.01	1.52	1.21	1.90	<0.01
1st Trimester	2.45	1.97	3.06	<0.01	2.58	2.07	3.22	<0.01	1.61	1.27	2.05	<0.01	1.58	1.23	2.03	<0.01
2nd Trimester	2.40	1.91	3.00	<0.01	2.53	2.02	3.18	<0.01	1.50	1.17	1.93	<0.01	1.48	1.15	1.91	<0.01
3rd Trimester	2.28	1.81	2.87	<0.01	2.43	1.92	3.06	<0.01	1.36	1.05	1.76	0.02	1.40	1.08	1.81	0.01
SSRIs (exposure extended by 60 days)																

During Pregnancy	2.07	1.56	2.75	<0.01	2.12	1.59	2.81	<0.01	1.19	0.88	1.61	0.26	1.04	0.76	1.42	0.80
1st Trimester	2.16	1.57	2.97	<0.01	2.22	1.62	3.06	<0.01	1.29	0.92	1.80	0.13	1.11	0.79	1.56	0.55
2nd Trimester	2.19	1.57	3.05	<0.01	2.27	1.63	3.17	<0.01	1.26	0.89	1.78	0.20	1.12	0.78	1.59	0.55
3rd Trimester	2.11	1.49	3.01	<0.01	2.17	1.52	3.08	<0.01	1.16	0.80	1.67	0.44	1.10	0.76	1.60	0.61
Non-SSRIs (exposure extended by 60 days)																
During Pregnancy	2.74	2.19	3.42	<0.01	2.93	2.35	3.67	<0.01	1.79	1.40	2.29	<0.01	1.77	1.38	2.29	<0.01
1st Trimester	2.95	2.27	3.84	<0.01	3.17	2.43	4.13	<0.01	2.01	1.52	2.66	<0.01	1.94	1.45	2.59	<0.01
2nd Trimester	2.64	2.01	3.46	<0.01	2.82	2.15	3.71	<0.01	1.68	1.26	2.25	<0.01	1.62	1.20	2.19	<0.01
3rd Trimester	2.60	1.98	3.40	<0.01	2.82	2.15	3.70	<0.01	1.59	1.19	2.13	<0.01	1.62	1.20	2.18	<0.01

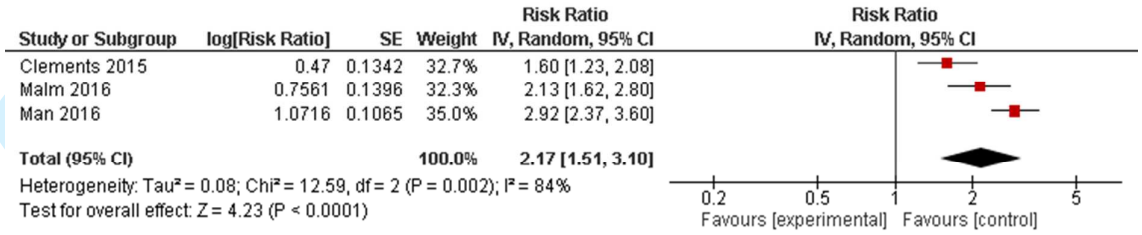
Supplementary material 8: Sensitivity analysis of excluding children with ADHD medication but without ADHD diagnosis

Exposure	Crude estimate			Model 1			Model 2			Model 3		
	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Antidepressants (excluded children with ADHD medication but no ADHD diagnosis)												
During Pregnancy	2.00	1.51 2.65	<0.01	2.14	1.61 2.84	<0.01	1.28	0.94 1.75	0.12	1.27	0.93 1.75	0.13
1st Trimester	2.09	1.49 2.92	<0.01	2.28	1.62 3.19	<0.01	1.41	0.98 2.02	0.06	1.38	0.96 2.00	0.09
2nd Trimester	1.96	1.33 2.88	<0.01	2.20	1.49 3.23	<0.01	1.27	0.85 1.91	0.25	1.28	0.85 1.93	0.25
3rd Trimester	2.18	1.53 3.10	<0.01	2.35	1.65 3.35	<0.01	1.33	0.91 1.94	0.14	1.37	0.34 2.01	0.11
SSRIs (excluded children with ADHD medication but no ADHD diagnosis)												
During Pregnancy	1.57	1.00 2.47	0.05	1.66	1.06 2.61	0.03	0.92	0.58 1.48	0.74	0.83	0.52 1.34	0.45
1st Trimester	1.65	0.98 2.79	0.06	1.79	1.06 3.03	0.03	1.03	0.60 1.77	0.91	0.94	0.54 1.62	0.81
2nd Trimester	1.66	0.89 3.09	0.11	1.80	0.97 3.36	0.06	1.00	0.53 1.88	1.00	0.94	0.49 1.78	0.84
3rd Trimester	1.48	0.77 2.84	0.24	1.55	0.81 2.98	0.19	0.83	0.43 1.62	0.59	0.80	0.41 1.56	0.51
Non-SSRIs (excluded children with ADHD medication but no ADHD diagnosis)												
During Pregnancy	2.46	1.79 3.39	<0.01	2.65	1.92 3.65	<0.01	1.62	1.15 2.29	<0.01	1.66	1.17 2.36	<0.01
1st Trimester	2.49	1.65 3.76	<0.01	2.72	1.81 4.11	<0.01	1.74	1.14 2.67	0.01	1.72	1.11 2.67	0.01
2nd Trimester	2.31	1.48 3.63	<0.01	2.63	1.67 4.13	<0.01	1.55	0.97 2.48	0.07	1.57	0.97 2.53	0.06
3rd Trimester	2.81	1.90 4.16	<0.01	3.05	2.06 4.53	<0.01	1.75	1.16 2.66	<0.01	1.84	1.21 2.79	<0.01

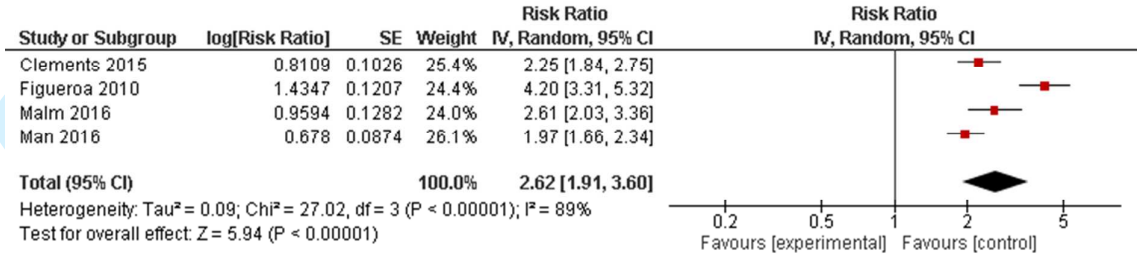
Supplementary material 9: Antidepressants user vs non-user (crude estimate)



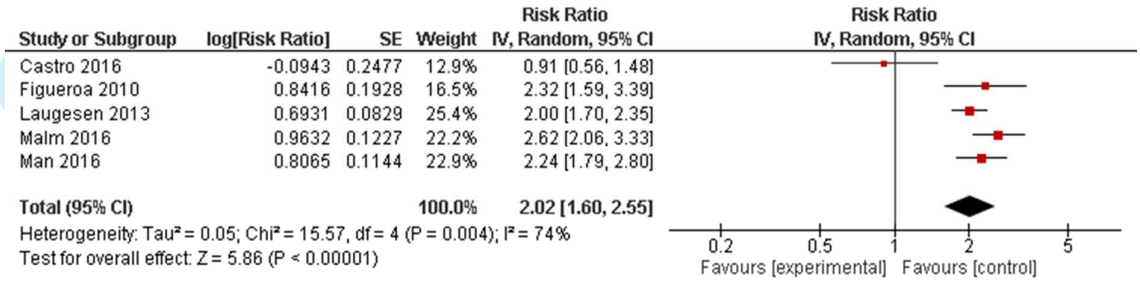
Supplementary material 10: Previous antidepressants user vs non-user (crude estimate)



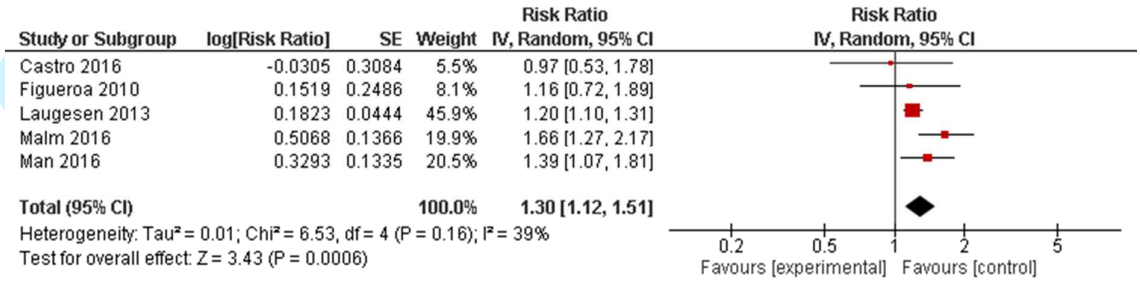
Supplementary material 11: Maternal psychiatric conditions (crude estimate)



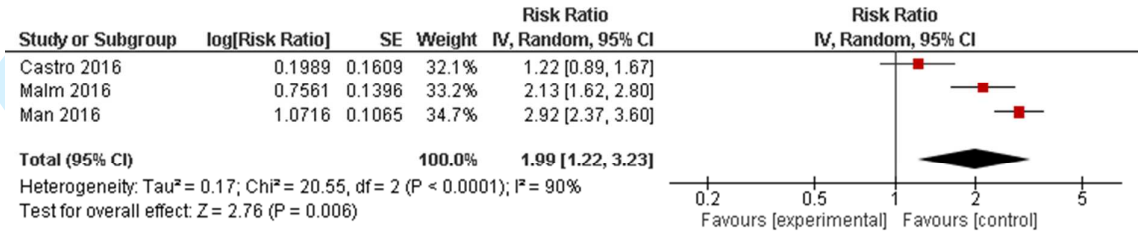
Supplementary material 12: Sensitivity Analysis of antidepressants user vs non-user (crude estimate)



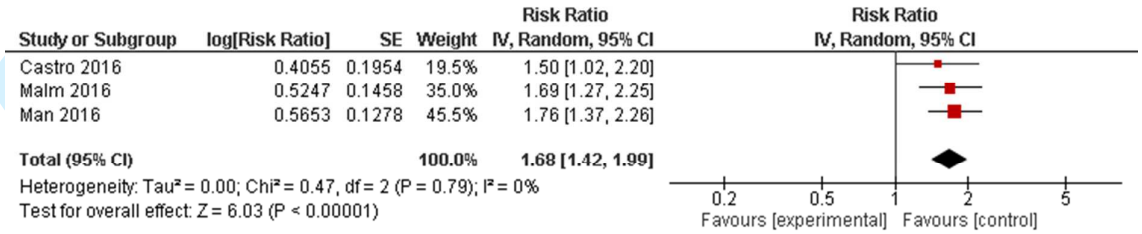
Supplementary material 13: Sensitivity Analysis of antidepressants user vs non-user (adjusted estimate)



Supplementary material 14: Sensitivity Analysis of previous antidepressants user vs non-user (crude estimate)



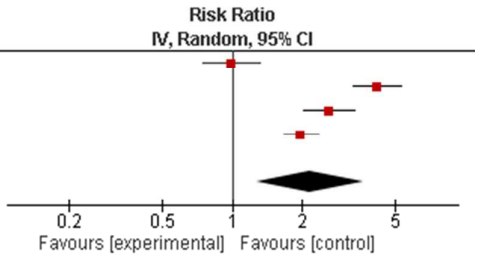
Supplementary material 15: Sensitivity Analysis of previous antidepressants user vs non-user (adjusted estimate)



Supplementary material 16: Sensitivity Analysis of maternal psychiatric conditions (crude estimate)

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Castro 2016	-0.0101	0.1417	24.5%	0.99 [0.75, 1.31]
Figueroa 2010	1.4347	0.1207	25.0%	4.20 [3.31, 5.32]
Malm 2016	0.9594	0.1282	24.8%	2.61 [2.03, 3.36]
Man 2016	0.678	0.0874	25.6%	1.97 [1.66, 2.34]
Total (95% CI)			**100.0%**	**2.16 [1.27, 3.66]**

Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 63.80$, df = 3 ($P < 0.00001$); $I^2 = 95\%$
Test for overall effect: $Z = 2.85$ ($P = 0.004$)



Supplementary material 17: Sensitivity Analysis of maternal psychiatric conditions (adjusted estimate)