Antidepressants during pregnancy and offspring autism: population-based cohort study

Journal:	*BMJ*
Manuscript ID	BMJ.2016.037083
Article Type:	Research
BMJ Journal:	BMJ
Date Submitted by the Author:	16-Dec-2016
Complete List of Authors:	Rai, Dheeraj; University of Bristol Lee, Brian; Drexel University School of Public Health, Department of Epidemiology and Biostatistics Dalman, Christina; Karolinska Institutet, Public Health Sciences Newschaffer, Craig; A.J. Drexel Autism Institute; Drexel University, School of Public Health Lewis, Glyn; UCL Psychiatric Epidemiology, Mental Health Sciences Unit Magnusson, Cecilia; Karolinska Institutet, Public Health Sciences
Keywords:	antidepressant, pregnancy, pharmacoepidemiology, autism, fetal safety, cohort study

Antidepressants during pregnancy and offspring autism: population-based cohort study

Dheeraj Rai[*1,2,3] consultant senior lecturer in psychiatry; **Brian K Lee**[*3,4,5] associate professor of epidemiology and biostatistics; **Christina Dalman**[3,6] professor of psychiatric epidemiology; **Craig Newschaffer**[4,5] professor of epidemiology; **Glyn Lewis**[7] professor of psychiatric epidemiology; **Cecilia Magnusson**[3,6] professor of epidemiology

1 Centre for Academic Mental Health, School of Social and Community Medicine, University of Bristol, Bristol, UK

2 Avon and Wiltshire Partnership NHS Mental Health Trust, Bristol, UK

3 Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden

4 Drexel University School of Public Health, Philadelphia, USA

5 AJ Drexel Autism Institute, Philadelphia, USA

6 Centre for Epidemiology and Community Medicine, Stockholm Health Care Services, Stockholm, Sweden

7 Division of Psychiatry, University College London, London, UK

*joint first authors

Correspondence to Dr Dheeraj Rai, Centre for Academic Mental Health, School of Social and Community Medicine, University of Bristol, Bristol, BS8 2BN, UK. Phone +441173313355, Email Dheeraj.rai@bristol.ac.uk

Word count: 3301 words

ABSTRACT

Objectives: To study the association between maternal antidepressant use during pregnancy with offspring autism spectrum disorder (ASD) using methods to account for confounding by indication.

Design: Observational prospective cohort study using regression methods, propensity score matching, sibling controls and negative control comparison.

Setting: Stockholm County, Sweden.

Participants: 254,610 individuals, including 5,378 with autism aged 4 to 17 years, residing in Stockholm County between 2001 and 2011 who were either exposed to antidepressants during pregnancy or to maternal psychiatric disorders but not antidepressants.

Exposure: Maternal antidepressant use recorded during first antenatal interview or prescription records.

Main outcome measure: Offspring diagnosis of ASD, with and without intellectual disability.

Results: Of the 3,342 children exposed to antidepressants during pregnancy, 4.1% (136) had an autism diagnosis, as compared to a 2.9% prevalence in 12,325 children unexposed to antidepressants whose mothers had a history of a psychiatric disorder (adjusted odds ratio 1.45, 95% CI 1.13 to 1.85). Propensity score analysis led to similar results, as did the sibling control analysis, although with wider confidence intervals. In a negative control comparison, there was no evidence of any increased risk of autism in children whose fathers were prescribed antidepressants during the mothers' pregnancy (1.13, 0.68 to 1.88). In all analyses, the risk increase concerned autism without but not with intellectual disability. We estimated that approximately 2% of autism cases would be prevented if no pregnant woman took antidepressants, assuming a causal, unconfounded association.

Conclusions: The association between antidepressant use during pregnancy and autism, particularly autism without intellectual disability may not solely be a by-product of confounding. Studying the potential underlying biological mechanisms may help the understanding of modifiable mechanisms in the aetiology of autism. Importantly, the absolute risk of autism was small, and hypothetically, if no pregnant women took antidepressants, the number of autism cases that could potentially be prevented would be very small.

INTRODUCTION

Depression is common in women of childbearing age, and between 3 to 8% pregnant women are prescribed antidepressants during pregnancy in Europe[1]. The fetal safety of antidepressant exposure during pregnancy has generated much debate following recent concerns of a possible association with autism in exposed offspring. In the last five years, 11 epidemiologic studies[2-11] have assessed the relationship between antidepressant use during pregnancy and offspring autism but robust conclusions have been elusive. Although most studies found evidence of unadjusted associations between antidepressants during pregnancy and autism outcomes, conclusions differed due to concerns about 'confounding by indication'. This was because depression or other psychiatric indications for antidepressant use could be associated with autism through genetic or non-genetic pathways, and thus the possibility of the observed associations representing the risk of autism due to the underlying indication for prescription could not be ruled out.

All antidepressants cross the placental barrier and are available to the developing fetus[12]. Most of the commonly used antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) increase the availability of serotonin in the synaptic cleft. The serotonergic system emerges early in embryogenesis, and is critical for neurodevelopment [13]. In-utero exposure to serotonergic antidepressants in animal models have reported associations with autism like behaviours in the offspring[14]. It is therefore biologically plausible that similar effects could be seen in humans. Disentangling a potential causal association of antidepressants on autism risk from that observed due to confounding by indication is crucial to reduce clinical uncertainty and help women make informed decisions regarding the risks and benefits of antidepressants during pregnancy.

However, in the absence of randomised controlled trials[7], observational studies are the only available source of making risk-benefit decisions in relation to antidepressant use during pregnancy. It is well known that such studies are prone to confounding bias, which may persist even after adjusting for multiple confounders[15-17]. Several approaches, such as propensity score matching, negative controls and sibling control designs have been suggested as strategies that may strengthen causal inference in observational studies[16], but remain largely unused in investigations of this issue. In order to help improve the understanding of the association between antidepressant use during pregnancy and offspring autism, our aim in this study was to apply a range of such causal analytic methods on data from a large, updated total population cohort in Stockholm County.

METHODS

The Stockholm Youth Cohort

We used data from the Stockholm Youth Cohort (SYC), an intergenerational record-linkage study comprising all individuals aged 0 to 17 years, residing in Stockholm County between 2001 and 2011 (n=735,096). It contains prospectively recorded data on the cohort members and their first-degree relatives collected by record linkage with a range of national and regional health-care, social and administrative registries[18 19]. The key for record linkage is the unique national identity numbers assigned to all Swedish residents. Figure 1 shows the derivation of the sample for our current analyses. We excluded cohort members born before 1996 since medication data were reliably collected only after this date. We also excluded individuals not linked to the medical birth register (such as those born abroad), those who could not be linked to their biological mothers, adopted children and those living in Stockholm County for less than 4 years. The residence requirement also allowed us to exclude children under 4 years in whom a diagnosis of autism may be less reliable.

Patient involvement:

As mandated by the ethical permission, no attempts were made to contact any cohort members for any aspect of this record linkage study. We will disseminate the results of this study to the public through presentations, social media and the press.

Medication use during pregnancy (exposure)

We derived information on maternal use of antidepressants in pregnancy from the Medical Birth Register (MBR, since 1997) and supplemented it with the Prescribed Drug Register (PDR, available from July 2005)[20 21]. The MBR contains information on current medications being taken as reported by pregnant women at their antenatal interview, at a median of 10 weeks gestation. The data are semi-automatically coded using World Health Organisation Anatomical Therapeutic classification (ATC) codes. It also contains free text data which we processed using a computerised search for generic drug names and Swedish and international brand names of antidepressants using fuzzy pattern matching to account for unknown abbreviations, non-standard terms, and misspellings[22]. The PDR contains data on drugs prescribed and dispensed in ambulatory care to the entire Swedish population and the medications are coded using ATC codes. In the PDR, we defined exposure to medication during pregnancy as a prescription up to 30 days prior to the start of the pregnancy (as estimated by the last menstrual period or ultrasonographic evidence) until the birth date of the child. We considered exposure to antidepressants if there was a record of these in either the MBR or the PDR to enable coverage of medication use during pregnancy throughout

across the multiple birth cohorts included in this study. The validity of these two data sources have been reported previously[20 21]. We cross-validated these two data sources in our sample as antidepressant use data were available in both registers for cohorts born in 2006 and 2007. Among these, 280 women out of 318 reporting antidepressant use in MBR were also recorded with antidepressant prescriptions during pregnancy in the PDR (88.1%).
We coded the medications as any antidepressant (ATC code N06A), and also divided them into selective serotonin reuptake inhibitors (SSRI, ATC N06AB), and all other antidepressants. We also categorised antidepressants based on their affinities for the serotonin transporter into high vs. medium or low affinity[2].

Ascertainment of autism (outcome)

We have described the multisource ascertainment of autism in previous publications[7 18 19]. In short, the vast majority of autism diagnoses in Sweden are provided via its free and universally accessible system of health and care. We collected diagnostic information from the relevant registers reflecting the pathways to diagnosis. These sources included autism diagnoses recorded in the National Patient Register, the Stockholm Child and Adolescent Mental Health Register and the Habilitation Registers [ICD-9 (299), ICD-10 (F84) or DSM-IV (299) codes]. We identified co-occurring intellectual disability using ICD 9 (317-319), ICD-10 (F70-79) and DSM-IV (317-319) in the child or adult mental health registers or the National patient register. We have previously carried out two validation procedures- a case-note validation study; and a cross-validation study of ASD diagnosis with a national twin study and found a high validity of the ASD diagnoses recorded in the registers[18].

Other variables

Depression and other psychiatric disorders in parents

We used ICD-9 and 10 diagnoses recorded in the National Patient Register, which covers inpatient (with complete national coverage since 1973), and outpatient specialist care (since 2001), to ascertain depression and other maternal and paternal diagnoses of psychiatric disorders as described elsewhere[23]. We supplemented these with diagnoses recorded from the Stockholm Adult Psychiatric Care Register which comprises all publically financed psychiatric care in Stockholm County (constituting 85% of all such care) since 1997[24].

We used prospectively collected data on maternal and paternal age at birth of child (continuous variables used as restricted cubic splines), quintiles of family income adjusted for year of ascertainment and family size, highest education of either parent (≤9 years, 10-12 years, ≥13 years), maternal country of birth (Sweden, Europe, other), parity (0, 1, 2 or more previous births) as potential confounders. We also used a number of other variables to

construct the propensity score as described below. These included maternal smoking and body mass index recorded at first antenatal visit, number of maternal depression diagnoses before birth, type of depression care (inpatient or outpatient) and a larger range of maternal neurologic and psychiatric conditions diagnosed before birth (see methods supplement).

Analysis

We used R-3.1.3 (R Foundation for Statistical Computing) for analysis. Following descriptive analyses, we used the following analytic strategies to assess the risk of offspring autism in mothers with antidepressant use during pregnancy:

Analysis 1: Risk estimates of autism in children of antidepressant users during pregnancy, compared to those with psychiatric disorders but no antidepressant use:
In our first analysis, we used logistic regression to derive odds ratios (OR) and their 95% confidence intervals (CI) as estimates of relative risks for autism in children of mothers who used antidepressants during pregnancy compared with those with a psychiatric disorder but no antidepressant use. We used this stringent comparison group to better account for confounding by indication and because women without any psychiatric disorder would be ineligible in hypothesised randomised controlled trials of this issue. We adjusted the model for birth year to control for period effects in medication use and autism ascertainment[19]. We then adjusted for the presence or absence of specific individual maternal psychiatric disorders (depression, anxiety disorder, bipolar disorder, non-affective psychotic disorders, obsessive-compulsive disorder, adjustment disorders, post traumatic stress disorders and other neurotic disorders) which are indications for antidepressant use (Model 2), and additionally for child sex, parental ages, birth order, maternal education, family income, and maternal country of birth (Model 3). We calculated population attributable fractions (PAF) using the fully adjusted model, estimating the proportion of autism cases that would be prevented if no women with psychiatric disorders were prescribed antidepressants, assuming a causal association and no residual confounding. In supplementary analysis, we restricted the above treatment group to mothers with antidepressant use who had a recorded psychiatric diagnosis. We also described the associations by the most commonly used individual antidepressants, and also grouped antidepressants as SSRI and non-SSRI's, and by their serotonin transporter receptor (SERT) affinity into high or low/medium SERT affinity.

Analysis 2: Propensity Score matched analysis:
In our second analysis, we calculated propensity score matched estimates for the above associations. Propensity score matching helps minimise the potential for confounding from

observed variables by comparing exposed and unexposed individuals with similar characteristics[25]. We estimated propensity scores for antidepressant use during pregnancy using a boosted classification and regression tree model[26], from the above covariates, and additional variables regarding maternal psychiatric disorders including indicators of severity such as the type of psychiatric care and number of previous care episodes for depression, and the use of other medications (see Methods Supplement). We matched children of women with and without antidepressant use using the propensity score using a maximum of 4:1 unexposed:exposed nearest neighbour matching with a caliper of 0.20 SD and exact matching on birth year, sex of child, and number of depression diagnoses. We estimated odds ratios and 95% CI from cluster robust logistic regression models.

Analysis 3: Outcome discordant matched sibling-sets analysis:
In our third analysis, we analysed associations of maternal antidepressant use in pregnancy with ASD in matched sets of outcome discordant siblings (i.e., sibling sets where there is at least 1 sibling with ASD and 1 sibling without ASD). Siblings share up to half of their genetic make-up and generally share their early postnatal environment. Sibling analysis can be a powerful method to control for unmeasured confounders, such as maternal genetic liability for neuropsychiatric conditions, when the confounders are shared more than the exposure[27]. We derived odds ratios and CI's using conditional logistic regression models adjusted for sex, parity, and birth year.

Analysis 4: comparison with risk estimates for paternal antidepressant use during pregnancy as a negative control:
In our fourth analysis, we used paternal use of antidepressant as a negative control exposure with the assumption that the fathers would share many of the unmeasured confounders with mothers, and if a similar heightened risk of autism were observable with paternal and maternal use of antidepressants, the associations would be unlikely to reflect an in-utero effect of the medications[28]. In these analyses, we used data for the individuals born in years 2006 and 2007 where we had data on antidepressant prescriptions for the mothers and fathers, and estimated the associations of antidepressant prescriptions in fathers during the time of the mother's pregnancy with the outcomes.

Sensitivity analysis:
In sensitivity analysis, we estimated how robust the estimates of associations between antidepressant exposure and ASD were to unmeasured confounding in our propensity score matched sample. We assumed a binary confounder *U* increased ASD risk and was more prevalent in antidepressant users than in non-antidepressant users. Given specified

parameters such as the relationship of *U* with ASD and the prevalence of *U* in antidepressant users and non-users, we estimated odds ratios and 95% CI corrected for this unmeasured confounder, specified over a range of plausible parameters[29].

RESULTS

The descriptive statistics of the cohort in relation to exposure to antidepressants during pregnancy or mental disorders are provided in Table 1. Of the 3,342 children exposed to antidepressants during pregnancy, 136 (4.1%) had an autism diagnosis. The comparison group included 12,325 children of mothers with a psychiatric disorder but no antidepressant use during pregnancy, of which 353 (2.9%) had an autism diagnosis. The majority of the cohort children (n=238,943) did not have a recorded maternal history of psychiatric disorder or antidepressant use during pregnancy and comprised 4,889 autism cases (2.1%).

Exposure to antidepressants during pregnancy was associated with higher odds of having an autism diagnosis than exposure to a maternal psychiatric disorder without antidepressants (adjusted OR 1.45, 95%CI 1.13 to 1.85, Table 2). This association was, observed only for autism without intellectual disability (1.57, 1.21 to 2.04). The results were similar when we restricted the antidepressant exposed group to mothers who had a recorded psychiatric diagnosis (Supplementary table S1). Assuming an unconfounded, causal association, the corresponding PAF suggested that approximately 2% of autism cases would be prevented if no pregnant woman with a psychiatric disorder took antidepressants [2.1% (-0.7-4.7%].

The propensity score analysis led to very similar results to those found using conventional regression models (Table 3). The numbers were smaller for the sibling control analyses, but results again appeared consistent although with wider confidence intervals which included 1 (Table 3). In our negative control analysis, there was no evidence of an increased risk of autism in children whose fathers were prescribed antidepressants during the mothers' pregnancy (adjusted OR 1.13 CI (0.68-1.88) but the association with maternal prescriptions for antidepressants continued to be observed [1.69 (1.06-2.72)] (Table 4). In all analyses, the risk estimates were greater for individuals without intellectual disability as compared to those with ID.

In sensitivity analysis, the results appeared to be moderately robust to unmeasured confounding (Supplementary Table 2). The rates and associations of autism in children

exposed to the most commonly prescribed individual antidepressants, also grouped into SSRI and non-SSRI antidepressants as well as by their serotonin receptor affinity are presented in Supplementary Tables 3 and 4. Although imprecision due to small numbers is evident, the rates of autism appeared to be higher in users of Clomipramine and Venlafaxine, and lowest in users of Paroxetine. Similar associations were observed for SSRI and non-SSRI antidepressants in relation to autism risk. The point estimates for the risk of autism in users of low/moderate SERT affinity appeared to be greater than that of users of high SERT affinity antidepressants although the confidence intervals overlapped. Finally, the results were similar to our main analysis when we repeated the analysis including

DISCUSSION

In this large Swedish population based study, we carried out several analyses to further understand the association between antidepressant use during pregnancy and offspring autism. The main findings were: children exposed to antidepressants during pregnancy appeared to be at a higher risk of autism, particularly autism with intellectual disability, than children exposed to psychiatric disorders without treatment with antidepressants. The findings appeared to be consistent across traditional regression methods, propensity score matching and a sibling set comparison, and maternal exposure to antidepressants had a strong association with the outcomes whereas no such association was observed with paternal exposure. This points to a potential effect of antidepressant use on autism risk beyond any effect due to confounding by the underlying condition. However, it is important to note that the absolute risk was small and 4.1% of children exposed to antidepressants in utero had autism as compared to 2.9% of those with a maternal history of psychiatric disorder. We estimated that only about 2% of autism cases in this population would be prevented, if the association was causal and no women with psychiatric disorders used antidepressants during pregnancy.

The main strengths of this study were the large sample size and the range of analyses carried out to strengthen causal inference beyond traditional methods. Since the study included the total population of Stockholm County, and benefited from multisource ascertainment of cases, as opposed to studies relying on hospital discharge diagnoses, the findings are likely to have high external validity. The possibility of exposure misclassification cannot be ruled out, but the availability of both self-report information from the medical birth register and dispensation information from the prescribed drug register was an advantage[20 21]. The absence of detailed measures of depression severity during pregnancy was a limitation and so we used propensity scores to match and therefore balance exposure

groups using a wide range of relevant characteristics. Due to small numbers, we were not able to assess trimester specific or dose response effects.

This study builds on our previous case-control study,[7] now enhanced with a larger sample, a more stringent comparison group of mothers with psychiatric disorders, and a range of causal inference methods to strengthen confidence in the results. Although a number of large register-based studies have been carried out to date, the number of autism cases exposed has been small and some studies appeared to have substantially under-ascertained autism. This has led to imprecise estimates, which have been pervasive in all studies on this topic, including those that have concluded that the association is likely to be explained by confounding[6 8]. Unlike some previous studies, we were unable to study discontinuation of antidepressants before pregnancy as an additional negative control since the prescribed drug register was only operation since 2005 and thus had insufficient numbers. It should be noted that since a large proportion of women discontinue medications[30], the cohorts that did have such data[2 10 11], had more statistical power to find an effect in the discontinuation group, as opposed to effects in those who continued the medication during pregnancy. The upper limits of the estimates of the associations reported in these studies were consistent with the results we report.

The different analyses we used have different strengths and limitations, but their findings appeared to triangulate, pointing towards an association between maternal antidepressant use in pregnancy and offspring autism. On the other hand, the increased risk was largely seen for autism without intellectual disability, a phenotype that has been shown to be more heritable[31], which may suggest a role for unmeasured genetic confounding. Furthermore, higher point estimates for lower SERT affinity antidepressants, several of which are prescribed for more severe depression[2], may suggest a role of confounding by severity of depression. We simulated the potential impact of unmeasured confounding which suggested that such an unmeasured confounder would have to be a strong risk factor for autism, exerting a confounding influence above and beyond the multiple covariates already controlled for in the propensity score matching. Taken together, it is difficult to conclusively dismiss the possibility of the observed associations to be wholly attributable to confounding.

So what should families and doctors making decisions about antidepressants during pregnancy make of such results? First, this and other studies clearly suggest that there is an increased background risk of autism in children of women with psychiatric conditions, regardless of antidepressant treatment. Second, despite the observed relative risks, over 95% of women who took antidepressants during pregnancy did not have a child with autism.

And finally, if a causal link were robustly established, and if no pregnant women took antidepressants during pregnancy, only 2% of autism cases in this population would be prevented. It is known that women may perceive such risks greater than they are,[32] and a balanced discussion in relation to clinical decision making in the light of evolving, but yet inconsistent evidence is important. On the other hand, given that this association may not solely be the by-product of confounding by indication, it is important to continue investigating possible underlying biological mechanisms which may help elucidate alternative autism prevention strategies.

Competing interests:

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Author contributions:

DR, BL and CM had the research idea, and CD, CN and GL helped with its development. DR wrote the first and subsequent drafts of the paper with important intellectual input from all co-authors. BL conducted the statistical analysis. All authors had full access to the data, specifically, the statistical reports and tables arising from the data. BL takes responsibility of the integrity of the data and accuracy of the data analysis. All authors have approved the final version of the manuscript submitted for publication.

DR, BL and CM are the guarantors and affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned have been explained.

Acknowledgements: We thank Michael Lundberg, data manager at Karolinska Institutet for help with data extraction.

Ethical approval

Ethical approval was obtained from the Research Ethics Committee at Karolinska Institutet, Stockholm [2013/1118-32].

Funding

Swedish Research Council (grant No 2012-3017).

Role of funders and sponsors

No funder had any role in the study design; data collection, analysis, or interpretation; in the writing of the report; or in the decision to submit the article for publication. The views expressed are those of the authors and not necessarily those of any of the funders or organisations they represent.

Data Sharing

No further data available.

Exclusive licence statement:

References

1. Charlton RA, Jordan S, Pierini A, et al. Selective serotonin reuptake inhibitor prescribing before, during and after pregnancy: a population-based study in six European regions. *BJOG* 2015;122(7):1010-20. doi: 10.1111/1471-0528.13143 [doi]

2. Clements CC, Castro VM, Blumenthal SR, et al. Prenatal antidepressant exposure is associated with risk for attention-deficit hyperactivity disorder but not autism spectrum disorder in a large health system. *Mol Psychiatry* 2014 doi: mp201490 [pii];10.1038/mp.2014.90 [doi]

3. Croen LA, Grether JK, Yoshida CK, et al. Antidepressant use during pregnancy and childhood autism spectrum disorders. *Arch Gen Psychiatry* 2011;68(11):1104-12. doi: archgenpsychiatry.2011.73 [pii];10.1001/archgenpsychiatry.2011.73 [doi]

4. Gidaya NB, Lee BK, Burstyn I, et al. In utero exposure to selective serotonin reuptake inhibitors and risk for autism spectrum disorder. *J Autism Dev Disord* 2014;44(10):2558-67. doi: 10.1007/s10803-014-2128-4 [doi]

5. Harrington RA, Lee LC, Crum RM, et al. Prenatal SSRI use and offspring with autism spectrum disorder or developmental delay. *Pediatrics* 2014;133(5):e1241-e48. doi: peds.2013-3406 [pii];10.1542/peds.2013-3406 [doi]

6. Hviid A, Melbye M, Pasternak B. Use of selective serotonin reuptake inhibitors during pregnancy and risk of autism. *N Engl J Med* 2013;369(25):2406-15. doi: 10.1056/NEJMoa1301449 [doi]

7. Rai D, Lee BK, Dalman C, et al. Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. *BMJ* 2013;346:f2059.

8. Sorensen MJ, Gronborg TK, Christensen J, et al. Antidepressant exposure in pregnancy and risk of autism spectrum disorders. *Clin Epidemiol* 2013;5:449-59. doi: 10.2147/CLEP.S53009 [doi];clep-5-449 [pii]

9. Boukhris T, Sheehy O, Mottron L, et al. Antidepressant Use During Pregnancy and the Risk of Autism Spectrum Disorder in Children. *JAMA Pediatr* 2016;170(2):117-24. doi: 2476187 [pii];10.1001/jamapediatrics.2015.3356 [doi]

10. Castro VM, Kong SW, Clements CC, et al. Absence of evidence for increase in risk for autism or attention-deficit hyperactivity disorder following antidepressant exposure during pregnancy: a replication study. *Transl Psychiatry* 2016;6:e708. doi: tp2015190 [pii];10.1038/tp.2015.190 [doi]

11. Malm H, Brown AS, Gissler M, et al. Gestational Exposure to Selective Serotonin Reuptake Inhibitors and Offspring Psychiatric Disorders: A National Register-Based Study. *J Am Acad Child Adolesc Psychiatry* 2016;55(5):359-66. doi: S0890-8567(16)30007-7 [pii];10.1016/j.jaac.2016.02.013 [doi]

12. Thompson BL, Levitt P, Stanwood GD. Prenatal exposure to drugs: effects on brain development and implications for policy and education. *Nat Rev Neurosci* 2009;10(4):303-12. doi: nrn2598 [pii];10.1038/nrn2598 [doi]

13. Lauder JM, Wallace JA, Krebs H. Roles for serotonin in neuroembryogenesis. *Adv Exp Med Biol* 1981;133:477-506.
14. Homberg JR, Schubert D, Gaspar P. New perspectives on the neurodevelopmental effects of SSRIs. *Trends Pharmacol Sci* 2010;31(2):60-65. doi: S0165-6147(09)00201-6 [pii];10.1016/j.tips.2009.11.003 [doi]
15. Davies NM, Taylor G, Taylor A, et al. Cardiovascular and neuropsychiatric risks of varenicline too good to be true? *Lancet Respiratory Medicine* 2015;In Press
16. Lewis SJ, Relton C, Zammit S, et al. Approaches for strengthening causal inference regarding prenatal risk factors for childhood behavioural and psychiatric disorders. *J Child Psychol Psychiatry* 2013;54(10):1095-108. doi: 10.1111/jcpp.12127 [doi]
17. Thomas KH, Martin RM, Davies NM, et al. Smoking cessation treatment and risk of depression, suicide, and self harm in the Clinical Practice Research Datalink: prospective cohort study. *BMJ* 2013;347:f5704.
18. Idring S, Rai D, Dal H, et al. Autism Spectrum Disorders in the Stockholm Youth Cohort: Design, Prevalence and Validity. *PLoS One* 2012;7(7): e41280 doi: doi:10.1371/journal.pone.0041280
19. Idring S, Lundberg M, Sturm H, et al. Changes in prevalence of autism spectrum disorders in 2001-2011: findings from the Stockholm youth cohort. *J Autism Dev Disord* 2015;45(6):1766-73. doi: 10.1007/s10803-014-2336-y [doi]
20. Kallen B, Nilsson E, Olausson PO. Antidepressant use during pregnancy: comparison of data obtained from a prescription register and from antenatal care records. *Eur J Clin Pharmacol* 2011;67(8):839-45. doi: 10.1007/s00228-011-1021-8 [doi]
21. Stephansson O, Granath F, Svensson T, et al. Drug use during pregnancy in Sweden - assessed by the Prescribed Drug Register and the Medical Birth Register. *Clin Epidemiol* 2011;3:43-50. doi: 10.2147/CLEP.S16305 [doi]
22. Peters L, Kapusnik-Uner JE, Nguyen T, et al. An approximate matching method for clinical drug names. *AMIA Annu Symp Proc* 2011;2011:1117-26.
23. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;11:450. doi: 1471-2458-11-450 [pii];10.1186/1471-2458-11-450 [doi]
24. Jorgensen L, Ahlbom A, Allebeck P, et al. The Stockholm non-affective psychoses study (snaps): the importance of including out-patient data in incidence studies. *Acta Psychiatr Scand* 2010;121(5):389-92. doi: ACP1500 [pii];10.1111/j.1600-0447.2009.01500.x [doi]
25. Stuart EA, Rubin DB. Best Practices in Quasi-Experimental Designs: Matching methods for causal inference. In: Osborne J, ed. Best Practices in Quantitative Social Science. Thousand Oaks, CA: Sage Publications 2007:155-76.

26. Lee BK, Lessler J, Stuart EA. Improving propensity score weighting using machine learning. *Stat Med* 2010;29(3):337-46. doi: 10.1002/sim.3782 [doi]

27. Frisell T, Oberg S, Kuja-Halkola R, et al. Sibling comparison designs: bias from non-shared confounders and measurement error. *Epidemiology* 2012;23(5):713-20. doi: 10.1097/EDE.0b013e31825fa230 [doi]

28. Smith GD. Negative control exposures in epidemiologic studies. *Epidemiology* 2012;23(2):350-51. doi: 10.1097/EDE.0b013e318245912c [doi];00001648-201203000-00027 [pii]

29. Lin DY, Psaty BM, Kronmal RA. Assessing the sensitivity of regression results to unmeasured confounders in observational studies. *Biometrics* 1998;54(3):948-63.

30. Petersen I, Gilbert RE, Evans SJ, et al. Pregnancy as a major determinant for discontinuation of antidepressants: an analysis of data from The Health Improvement Network. *J Clin Psychiatry* 2011;72(7):979-85. doi: 10.4088/JCP.10m06090blu [doi]

31. Robinson EB, Samocha KE, Kosmicki JA, et al. Autism spectrum disorder severity reflects the average contribution of de novo and familial influences. *Proc Natl Acad Sci U S A* 2014;111(42):15161-65. doi: 1409204111 [pii];10.1073/pnas.1409204111 [doi]

32. Petersen I, McCrea RL, Lupattelli A, et al. Women's perception of risks of adverse fetal pregnancy outcomes: a large-scale multinational survey. *BMJ Open* 2015;5(6):e007390. doi: 10.1136/bmjopen-2014-007390

Table 1: Selected characteristics of the Stockholm Youth Cohort (N, %)

	Antidepressant exposed during pregnancy (N = 3,342)	Maternal psychiatric disorder and unexposed to antidepressants (N = 12,325)	No maternal psychiatric disorder and unexposed to antidepressants (N = 238,943)
Autism Spectrum Disorder (ASD) ASD without ID ASD with ID	136 (4.1) 122 (3.7) 14 (0.4)	353 (2.9) 291 (2.4) 62 (0.5)	4,889 (2.1) 3,835 (1.6) 1,054 (0.4)
Maternal age, mean (SD)	31.7 (5.2)	31.5 (5.4)	30.7 (5.0)
Paternal age, mean (SD)	34.0 (6.4)	34.0 (6.6)	33.7 (6.1)
Male child	1,727 (51.7)	6,446 (52.3)	122,354 (51.2)
Parity 1 2 3+	 1,673 (50.1) 951 (28.4) 718 (21.5)	 5,203 (42.2) 4,248 (34.5) 2,874 (23.3)	 108,192 (45.3) 87,765 (36.7) 42,986 (18.0)
Maternal education > 12 years	1,382 (41.3)	4,897 (39.7)	110,017 (46.0)
Family income, highest quintile	904 (27.1)	3,306 (26.8)	83,190 (34.8)
Maternal birth country, Sweden	2,713 (81.2)	9,176 (74.5)	177,395 (74.2)
Maternal smoking	512 (15.3)	1,434 (11.6)	16,996 (7.1)
Maternal BMI at 1st antenatal visit Normal (18.5≤BMI<25) Underweight (BMI <18.5) Overweight (25≤BMI<30) Obese (BMI ≥30) Missing	 1,741 (52.1) 81 (2.4) 619 (18.5) 328 (9.8) 573 (17.2)	 6,035 (49.0) 316 (2.6) 2,272 (18.4) 981 (8.0) 2,721 (22.1)	 129,597 (54.2) 5,590 (2.3) 40,212 (16.8) 13,945 (5.8) 49,599 (20.8)
Maternal lifetime psychiatric diagnoses before birth Depression Anxiety disorder Bipolar disorder Non-affective psychoses Obsessive-compulsive disorder	 1,378 (41.3) 685 (20.5) 70 (2.1) 46 (1.4) 56 (1.7)	 5,800 (47.1) 2,594 (21.1) 402 (3.3) 645 (5.2) 139 (1.1)	 - - - - - -

Stress-related disorders	389 (11.7)	4,261 (34.6)	-
Other neurotic disorders	89 (2.7)	1,202 (9.8)	
N, maternal depression diagnoses before birth			
0	1,964 (58.8)	6,525 (52.9)	238,943 (100)
1	517 (15.5)	3,287 (26.7)	-
2	240 (7.2)	1,128 (9.2)	-
3	172 (5.2)	508 (4.1)	-
4+	449 (13.4)	877 (7.1)	-
N, maternal depression diagnoses before birth by dx type			
Specialist care			
0	2,337 (69.9)	8,018 (65.1)	238,943 (100)
1	388 (11.6)	2,493 (20.2)	-
2	199 (6.0)	952 (7.7)	-
3+	418 (12.5)	862 (7.0)	-
Primary care			
0	3,059 (91.5)	11,766 (95.5)	238,943 (100)
1	129 (3.9)	286 (2.3)	-
2+	154 (4.6)	273 (2.2)	-
Inpatient diagnosis			
0	2,982 (89.2)	10,938 (88.8)	238,943 (100)
1	229 (6.9)	969 (7.9)	-
2	70 (2.1)	233 (1.9)	-
3+	61 (1.8)	184 (1.5)	-
Other			
0	3,201 (95.8)	12,042 (97.7)	238,943 (100)
1	105 (3.1)	232 (1.9)	-
2+	36 (1.1)	51 (0.4)	-
Medications during pregnancy			
SSRI antidepressants	2,710 (81.1)	-	-
Non-SSRI antidepressants	723 (21.6)	-	-
Antiepileptics	37 (1.1)	73 (0.6)	490 (0.2)
Antipsychotics	106 (3.2)	166 (1.4)	347 (0.2)
Anxiolytics	314 (9.4)	191 (1.6)	337 (0.1)

Table 2: Regression-estimated odds ratios and 95% CI for associations of antidepressant use during pregnancy and ASD when comparing children exposed prenatally to antidepressants with children exposed to maternal psychiatric disorders but no antidepressants (combined N = 15,667).

Outcome (N exposed cases)	**Model 1**	**Model 2**	**Model 3**
ASD (136)	**1.47 (1.20, 1.81)**	**1.47 (1.16, 1.87)**	**1.45 (1.13, 1.85)**
ASD without ID (122)	**1.59 (1.28, 1.98)**	**1.62 (1.25, 2.08)**	**1.57 (1.21, 2.04)**
ASD with ID (14)	0.87 (0.49, 1.57)	0.81 (0.39, 1.68)	0.72 (0.38, 1.77)

ID = intellectual disability
Cluster robust logistic regression models (cluster = birth mother)
Model 1: adjusted for birth year
Model 2: Model 1 + maternal psychiatric disorders diagnosed before birth (depression, anxiety disorder, bipolar disorder, non-affective psychotic disorders, obsessive-compulsive disorder, stress-related disorders, other neurotic disorders), maternal medications used during pregnancy (anti-epileptics, anti-psychotics, anxiolytics)
Model 3: Model 2 + sex, maternal age, paternal age, parity, maternal education, family income, maternal birth country

Table 3: Matching-estimated odds ratios and 95% CI for associations of antidepressant use during pregnancy and ASD

Outcome	Propensity score matched OR (95% CI)	Sibling matched OR (95% CI)
ASD	**1.54 (1.15, 2.08)**	1.36 (0.84, 2.20)
ASD without ID	**1.61 (1.17, 2.22)**	1.57 (0.92, 2.66)
ASD with ID	1.18 (0.52, 2.66)	0.78 (0.24, 2.54)

ID = intellectual disability

Propensity score matched estimates of associations of antidepressant use during pregnancy and ASD, when comparing children exposed prenatally to antidepressants with children exposed to maternal psychiatric disorder but no antidepressants.

Outcome-discordant sibling matched estimates for associations of antidepressant use during pregnancy and ASD. Conditional logistic regression models adjusted for sex, parity, and birth year.

For additional details, see the Methods Supplement.

Table 4: Negative control analysis: odds ratios and 95% CI for associations of National Prescription Drug Register-ascertained parental antidepressant use and parental depression history in the Stockholm Youth Cohort subsample born 2006-2007 (subsample N = 47,629)

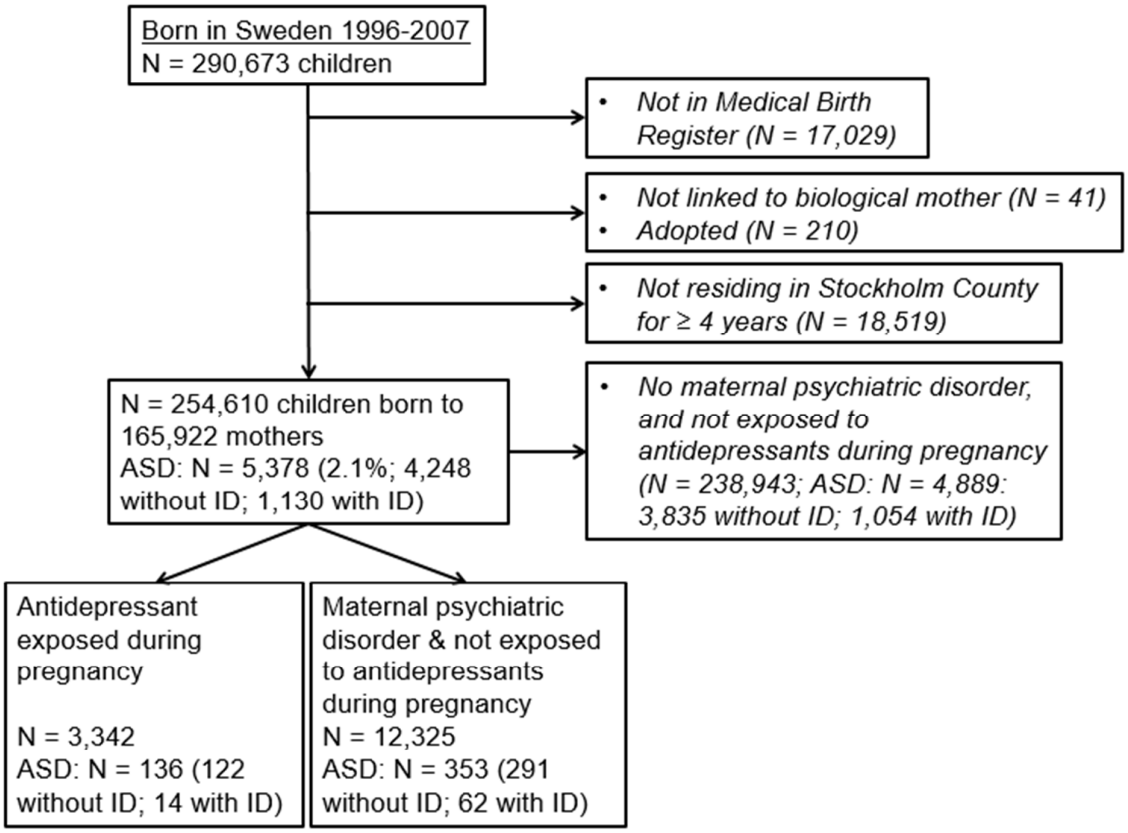
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)**
ASD		
Maternal antidepressant use	**2.01 (1.34, 3.01)**	**1.69 (1.06, 2.72)**
Paternal antidepressant use	1.38 (0.90, 2.12)	1.13 (0.68, 1.88)
ASD without ID		
Maternal antidepressant use	**2.27 (1.49, 3.47)**	**1.85 (1.11, 3.09)**
Paternal antidepressant use	1.46 (0.92, 2.32)	1.18 (0.68, 2.06)
ASD with ID		
Maternal antidepressant use	0.86 (0.21, 3.49)	0.83 (0.25, 2.82)
Paternal antidepressant use	1.03 (0.32, 3.24)	0.91 (0.26, 3.27)

Antidepressant exposure defined as ever/never during pregnancy if a prescription was dispensed from 30 days prior to conception until birth

ID = intellectual disability

Cluster robust logistic regression models (cluster = birth mother). Covariates in adjusted models are birthyear, maternal and paternal antidepressant use, maternal and paternal depression before birth, maternal age, sex, paternal age, parity, maternal education, family income quintile, maternal birth country, and other maternal psychiatric disorders before birth (anxiety disorder, bipolar disorder, non-affective psychotic disorders, obsessive-compulsive disorder, stress-related disorders, other neurotic disorders)

Figure 1: Sample derivation for the Stockholm Youth Cohort



Rai, Lee et al. Antidepressants during pregnancy and offspring autism: population-based cohort study

Methods supplement and supplementary tables

Methods Supplement

Propensity score matching

Propensity scores were estimated using a boosted classification and regression tree model from: maternal age, sex, birth year, parity, maternal education, family income, maternal country of origin, maternal smoking at first antenatal visit, maternal body mass index at first antenatal visit, number and type of depression diagnoses (specialist care, primary care, inpatient care), and maternal neurologic and psychiatric conditions diagnosed before birth: (alcohol misuse, anxiety, bipolar disorder, obsessive-compulsive disorder, depression, drug misuse, non-affective psychotic disorders, other childhood disorders, other neurotic disorders, personality disorders, stress-related disorders, benign intercranial hypertension, bell's palsy, cerebrovascular disease, cerebral palsy, epilepsy, headache, migraine, myasthenia gravis, multiple sclerosis), and medications taken during pregnancy (anti-epileptics, anti-psychotics, and anxiolytics). Propensity score matching of exposed and unexposed persons was carried out using a maximum of 4:1 unexposed:exposed nearest neighbor matching with a caliper of 0.20 SD and exact matching on birth year, sex of child, and number of depression diagnoses. Odds ratios and 95%CI are estimated from cluster robust logistic regression models.

Propensity score matched analyses for ASD, ASD without ID, and ASD with ID were based on the following number of exposed cases, respectively: 204 ASD cases, of whom 68 were exposed; 175 ASD without ID cases, of whom 60 were exposed; 29 ASD with ID cases, of whom 8 were exposed.

Sibling matching

Sibling matched analyses for ASD, ASD without ID, and ASD with ID were based on the following, respectively: 3,038 ASD cases, of whom 66 were exposed, and 94 sibling sets with discordant outcomes and discordant exposures; 2,408 ASD without ID cases, of whom 60 were exposed, and 81 sibling sets with discordant outcomes and discordant exposures; 630 ASD with ID cases, of whom 6 were exposed; 14 sibling sets with discordant outcomes and discordant exposures.

Supplementary Table 1: Regression-estimated odds ratios and 95% CI for associations of antidepressant use during pregnancy and ASD when comparing children exposed prenatally to antidepressants *prescribed for a known psychiatric condition* with children exposed to maternal psychiatric disorders but no antidepressants.

Outcome (N exposed cases)	Model 1	Model 2	Model 3
ASD (75)	**1.72 (1.32, 2.24)**	**1.53 (1.15, 2.05)**	**1.48 (1.11, 1.99)**
ASD without ID (66)	**1.80 (1.36, 2.40)**	**1.65 (1.21, 2.25)**	**1.57 (1.15, 2.15)**
ASD with ID (9)	1.27 (0.63, 2.53)	0.99 (0.44, 2.21)	0.97 (0.41, 2.28)

ID = intellectual disability
Cluster robust logistic regression models (cluster = birth mother)
Model 1: adjusted for birth year
Model 2: Model 1 + maternal psychiatric disorders diagnosed before birth (depression, anxiety disorder, bipolar disorder, non-affective psychotic disorders, obsessive-compulsive disorder, stress-related disorders, other neurotic disorders), maternal medications used during pregnancy (anti-epileptics, anti-psychotics, anxiolytics)
Model 3: Model 2 + sex, maternal age, paternal age, parity, maternal education, family income, maternal birth country

Supplementary Table 2: Sensitivity of model results to unobserved confounding at specified parameter levels.

Increase in risk of ASD on account of unmeasured confounder*	Prevalence of unmeasured confounder in exposed	Prevalence of unmeasured confounder in unexposed	Corrected OR (95% CI)
-	0	0	**1.61 (1.17, 2.22)****
Doubled	10%	5%	1.54 (1.12, 2.12)
Doubled	20%	10%	1.48 (1.07, 2.03)
Doubled	30%	10%	1.36 (0.99, 1.88)
Doubled	40%	10%	1.27 (0.92, 1.74)
Doubled	50%	10%	1.18 (0.86, 1.63)
Tripled	10%	5%	1.48 (1.07, 2.03)
Tripled	20%	10%	1.38 (1.00, 1.90)
Tripled	30%	10%	1.21 (0.88, 1.67)
Tripled	40%	10%	1.07 (0.78, 1.48)
Tripled	50%	10%	0.97 (0.70, 1.33)

* assuming that the elevated risk of ASD due to *U* is consistent in both the exposed and the unexposed

** the original Table 3 propensity-score matched estimate of the OR and 95% CI for exposure to antidepressants during pregnancy and risk of ASD without intellectual disability

Odds ratios and 95% confidence intervals are calculated based on formulae provided by Lin et al., Biometrika 1998 http://www.jstor.org/stable/2533848

Supplementary Table 3: ASD rates by the most commonly prescribed antidepressants during pregnancy in the Stockholm Youth Cohort

Antidepressant	N exposed to drug	N, ASD cases (%)	N, ASD without ID (%)
Fluoxetine	453	16 (3.5%)	15 (3.3%)
Citalopram	1064	52 (4.9%)	46 (4.3%)
Paroxetine	264	5 (1.9%)	4 (1.5%)
Sertraline	912	31 (3.4%)	27 (3.0%)
Clomipramine	235	16 (6.8%)	15 (6.4%)
Venlafaxine	213	11 (5.2%)	11 (5.2%)
Any SSRI AD	2710	105 (3.9%)	93 (3.4%)
Any non-SSRI AD	723	32 (4.4%)	30 (4.1%)
High SERT affinity AD	1928	70 (3.6%)	63 (3.3%)
Low/moderate SERT affinity AD	1414	66 (4.7%)	59 (4.2%)

Note: Other antidepressants included were Fluvoxamine, Escitalopram, Amitryptiline, Mirtazapine, Bupropion and Duloxetine but results not presented since cell sizes for exposure or outcome group were <5.

AD = antidepressant; ID = intellectual disability; SERT = serotonin transporter

High SERT affinity antidepressants: escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, clomipramine

Low/moderate SERT affinity antidepressants: citalopram, fluvoxamine, venlafaxine, amitriptyline, mirtazapine, bupropion

Supplementary Table 4: Odds ratios and 95% confidence intervals[1] for associations of the most commonly prescribed antidepressants during pregnancy and ASD in the Stockholm Youth Cohort

Antidepressant	ASD OR (95% CI)	ASD without ID OR (95% CI)
Fluoxetine	1.42 (0.84, 2.39)	1.59 (0.92, 2.73)
Citalopram	1.65 (1.20, 2.26)	1.75 (1.25, 2.45)
Paroxetine	0.61 (0.25, 1.49)	0.60 (0.22, 1.62)
Sertraline	1.45 (0.98, 2.16)	1.52 (0.99, 2.32)
Clomipramine	1.76 (1.01, 3.05)	2.07 (1.17, 3.64)
Venlafaxine	1.81 (0.89, 3.71)	2.14 (1.05, 4.37)
Any SSRI antidepressant	1.45 (1.14, 1.83)	1.54 (1.20, 1.97)
Any non-SSRI antidepressant	1.53 (1.03, 2.28)	1.74 (1.15, 2.63)
High SERT affinity AD	1.33 (1.02, 1.73)	1.45 (1.09, 1.92)
Low/moderate SERT affinity AD	1.71 (1.30, 2.24)	1.84 (1.38, 2.46)

AD = antidepressant; ID = intellectual disability; SERT = serotonin transporter

[1]OR and 95% CI compare persons exposed to the specific antidepressant against persons unexposed to any antidepressant but who have a prior maternal diagnosis of depression, anxiety disorder, bipolar disorder, non-affective psychoses, obsessive-compulsive disorder, stress-related disorders, or other neurotic disorders. Models are adjusted for birth year, maternal depression, and antidepressant polypharmacy (binary variable for use of 2 or more antidepressants).

High SERT affinity antidepressants: escitalopram, fluoxetine, paroxetine, sertraline, duloxetine, clomipramine; Low/moderate SERT affinity antidepressants: citalopram, fluvoxamine, venlafaxine, amitriptyline, mirtazapine, bupropion